

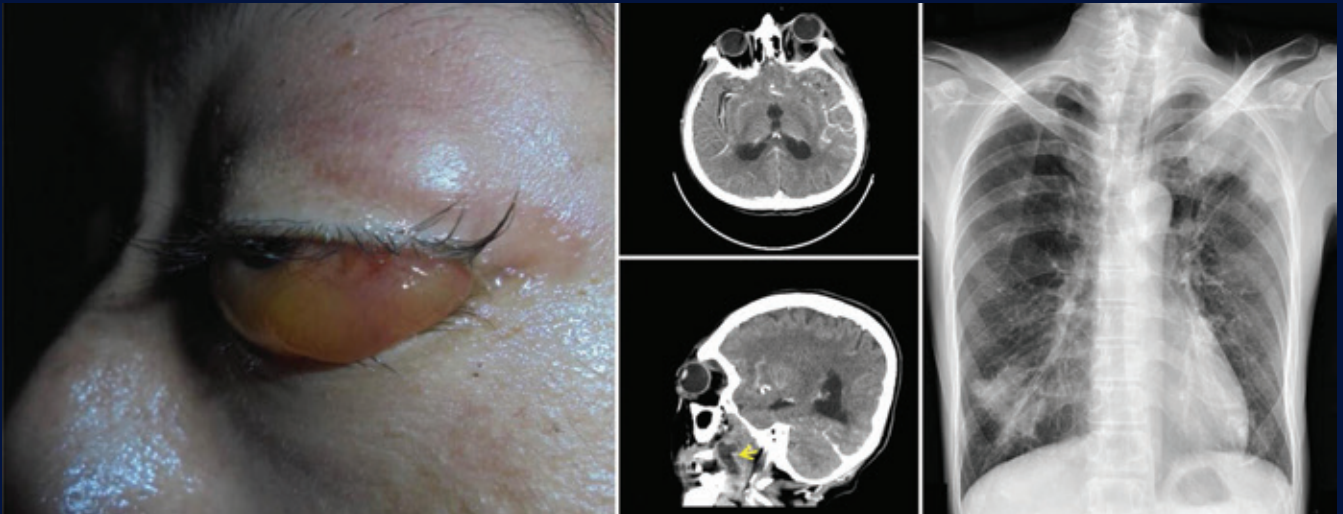
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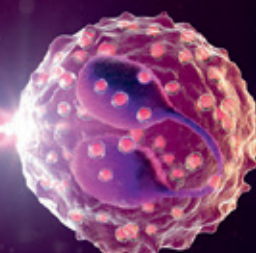
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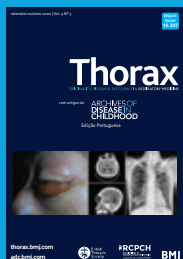
1. Ferguson et al., "Single-Use Autoinjector Functionality And Reliability For At-Home Administration Of Benralizumab For Patients With Severe Asthma: GRECO Trial Results", Journal of Asthma and Allergy 2019;12 363–373;
2. RCM de Fasenra consultado a 24/07/2020 em www.infarmed.pt.

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Este medicamento está sujeito a monitorização adicional. Isto irá permitir a rápida identificação de nova informação de segurança. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas através do Sítio da internet: <http://www.infarmed.pt/web/infarmed/submissaoam> (preferencialmente) ou através dos seguintes contactos: Direção de Gestão do Risco de Medicamentos: (Tel: +351 21 798 73 73; Linha do medicamento: 800222444 (gratuita); E-mail: farmacovigilancia@infarmed.pt). **Fasenra 30 mg solução injetável em caneta pré-cheia.** Cada caneta pré-cheia contém 30 mg de benralizumab* em 1 ml. *Benralizumab é um anticorpo monoclonal humanizado produzido por tecnologia de ADN recombinante em células ovárias do hamster chinês. Solução injetável em caneta pré-cheia (injetável) (Fasenra Pen). Solução clara a opalescente, incolor a amarela e pode conter partículas translúcidas ou brancas a esbranquiçadas. **Indicações terapêuticas:** Fasenra é indicado como tratamento adjuvante de manutenção em doentes adultos com asma eosinofílica grave, inadequadamente controlada apesar das doses elevadas de corticosteroides inalados em associação a agonistas-β de longa duração de ação. **Posologia e modo de administração:** O tratamento com Fasenra deve ser iniciado por um médico com experiência no diagnóstico e tratamento da asma grave. Após o treino adequado da técnica de injeção subcutânea e educação sobre sinais e sintomas de reações de hipersensibilidade, os doentes sem história conhecida de ocorrência de anafilaxia, ou os seus cuidadores, podem administrar Fasenra se o seu médico considerar apropriado, com seguimento médico se necessário. A autoadministração só deve ser considerada em doentes tratados anteriormente com Fasenra. **Posologia:** A dose recomendada de benralizumab é 30 mg administrados por injeção subcutânea a cada 4 semanas para as primeiras 3 doses, e depois a cada 8 semanas. Se uma injeção não for administrada na data planeada, a dose deve ser administrada assim que possível de acordo com o regime indicado; não deve ser administrada uma dose a duplicar. Fasenra destina-se ao tratamento de longa duração. A decisão de continuar a terapêutica deve ser efetuada pelo menos uma vez por ano, com base na severidade da doença, no nível de controlo das exacerbações e na contagem sanguínea de eosinófilos. Não é necessário qualquer ajuste de dose em doentes idosos ou em doentes com compromisso da função renal ou hepática. **População pediátrica:** A segurança e eficácia de Fasenra em crianças com 6 a 18 anos de idade não foram estabelecidas. Não estão disponíveis dados em crianças com 6 a 11 anos de idade. Os dados atualmente disponíveis em crianças com 12 a 18 anos de idade encontram-se descritos nas secções 4.8, 5.1 e 5.2 do RCM mas não pode ser feita qualquer recomendação posológica. **Modo de administração:** Fasenra é administrado por injeção subcutânea. Deve ser injetado na coxa ou abdómen. Se o profissional de saúde ou o cuidador administrar a injeção, esta pode ser efetuada na parte superior do braço. Não deve ser injetado em áreas onde a pele está sensível, ferida, eritematosa ou endurecida. **Contraindicações:** Hipersensibilidade à substância ativa ou a qualquer um dos excipientes. **Advertências e precauções especiais de utilização:** Fasenra não deve ser utilizado para tratar exacerbações agudas da asma. Os doentes devem ser informados a procurar aconselhamento médico se a sua asma permanecer não controlada ou se agravar após o início do tratamento. A descontinuação abrupta de corticosteroides após o início do tratamento com Fasenra não é recomendada. Se necessário, a redução das doses de corticosteroides deve ser gradual e efetuada sob supervisão de um médico. **Reações de hipersensibilidade:** Após a administração de benralizumab ocorreram reações sistémicas agudas, incluindo reações anafiláticas e reações de hipersensibilidade (por exemplo, urticária, urticária papular, erupção cutânea). Estas reações podem ocorrer horas após a administração, mas em alguns casos tiveram um início tardio (i.e. dias). História de anafilaxia não relacionada com benralizumab pode ser um fator de risco para a ocorrência de anafilaxia após a administração de Fasenra. Os doentes devem ser monitorizados por um período de tempo adequado após a administração de Fasenra, de acordo com a prática clínica. Em caso de reação de hipersensibilidade, Fasenra deve ser descontinuado permanentemente e deve ser iniciado o tratamento adequado. **Infecção parasitária (Helmíntica):** Os eosinófilos podem estar envolvidos na resposta imunitária a algumas infeções helmínticas. Os doentes com infeções helmínticas conhecidas foram excluídos da participação nos ensaios clínicos. Desconhece-se se Fasenra pode influenciar uma resposta do doente contra infeções helmínticas. Os doentes com infeções helmínticas pré-existentes devem ser tratados antes de iniciar o tratamento com Fasenra. Se os doentes ficarem infetados durante o tratamento com Fasenra e não responderem ao tratamento anti-helmíntico, o tratamento com Fasenra deve ser descontinuado até a infeção se resolver. **Interações medicamentosas e outras formas de interação:** Em doentes com idades compreendidas entre 12 e 21 anos com asma grave, a resposta humoral induzida pela vacinação contra o vírus da gripe sazonal não parece ser afetada pelo tratamento com benralizumab. Não é esperado um efeito de benralizumab na farmacocinética de medicamentos administrados concomitantemente. As enzimas do citocromo P450, bombas de efluxo e os mecanismos de ligação a proteínas não estão envolvidos na depuração de benralizumab. Não existe evidência da expressão de IL-5Rα nos hepatócitos. A depleção de eosinófilos não produz alterações sistémicas crónicas das citocinas pró-inflamatórias. **Efeitos indesejáveis:** **Frequentes:** Faringite, Reações de hipersensibilidade, Cefaleia, Pirexia, Reação no local de injeção; **Desconhecida:** Reação anafilática. **Titular da Autorização de Introdução no Mercado:** AstraZeneca AB, SE-151 85 Södertälje, Suécia. **Representante local do Titular da Autorização de Introdução no Mercado:** AstraZeneca Produtos Farmacêuticos, Lda., Rua Humberto Madeira, 7, Queluz de Baixo, 2730-097 Barcarena. Informações revistas em julho de 2020. Para mais informações deverá contactar o representante local do titular da Autorização de Introdução no Mercado. Medicamento de receita médica restrita, de utilização reservada a certos meios especializados. Financiada no âmbito da avaliação prévia à utilização hospitalar. Versão 1.0 (julho 2020).

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Contribuinte N.º PT 502 942 240 | Capital Social 1.500.000 €
PT-7378 aprovado a 07/08/2020



Journal of the British Thoracic Society
Impact Factor: 8.834
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ISSN: 0040-6376 (print)
ISSN: 1468-3296 (online)
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**Archives of
Disease in Childhood**

Edição bimestral em língua portuguesa
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ISSN: 0003-9888 (print)

ISSN: 1468-2044 (online)

Impact factor: 3.158

Journal of the Royal College of

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Editorial

Num momento em que a pandemia COVID-19 se expande, nomeadamente no nosso país, assumindo um desafio constante ao sistema de saúde e à sociedade em geral, e que tem levado à instituição de várias medidas que visam limitar o seu impacto, trazemos para Vossa leitura uma nova seleção de artigos editados nas revistas *Thorax* e *Archives of Disease in Childhood*.

E antes de realçar os artigos que incluímos, gostávamos de destacar a iniciativa do *BMJ* em promover um *Coronavirus Hub* (bmj.com/coronavirus), de acesso livre, onde estão depositados os artigos relacionados que são publicados em mais de 70 das suas revistas, contribuindo assim para um amplo acesso a mais uma significativa fonte de conhecimento.

Neste número inicialmente destacamos artigos focados na idade pediátrica, nomeadamente a investigação de Ploton D-C e colaboradores sobre patogénios respiratórios e síndrome torácica aguda em crianças com doença falciforme. Num estudo de coorte, observacional, prospetivo, que incluiu 101 crianças, os autores encontraram que a deteção viral em crianças febris com doença falciforme é frequente, mas a sua associação com a síndrome torácica aguda não foi estatisticamente demonstrada, embora os vírus de parainfluenza se revelassem duas vezes mais comuns, sendo a infeção por *M. pneumoniae* rara neste estudo, recomendando-se que uma eventual antibioterapia deva ser suportada pela identificação deste microrganismo intra-celular.

Igualmente na idade pediátrica, num estudo que nos chega de Singapura, Krishnan SG e colaboradores, confirmaram que a deteção visual qualitativa do pulso paradoxal (PP) no oxímetro de pulso poderá contribuir para prever resultados para crianças com dificuldade respiratória moderada a grave no contexto da urgência, nomeadamente na resposta à terapêutica inicial.

Numa revisão sistemática com meta-análise centrado na Doença Pulmonar Obstrutiva Crónica (DPOC), Loughran K e colaboradores, na ausência de informação suficiente, procuraram quantificar a extensão da deficiência de equilíbrio na DPOC e estabelecer os seus fatores clínicos contribuintes. Os autores incluíram vinte e três estudos ($n=2751$), encontrando que em comparação com controlos saudáveis, as pessoas com DPOC apresentam uma redução do equilíbrio clinicamente significativa, que pode estar relacionada com a redução da força muscular, da atividade física e da capacidade de exercício, reforçando a necessidade de se aumentar o foco sobre a reabilitação pulmonar de modo a incluir a avaliação do equilíbrio e o treino e a explorar mais a deficiência de equilíbrio na DPOC. Nas condições atuais relacionadas com a pandemia, devemos estar conscientes das limitações dos programas de reabilitação que não estarão acessíveis a um número significativo de doentes com doenças respiratórias crónicas, não permitindo atuar de acordo com a melhores práticas.

Realçando a relevância dos estudos funcionais respiratórios na avaliação clínica de múltiplas patologias, Balata H e colaboradores no Reino Unido, demonstram que a inclusão da espirometria num programa comunitário de rastreio de cancro do pulmão é viável e identifica um número significativo de indivíduos com obstrução do fluxo aéreo sem diagnóstico prévio, e inclusive, sem sintomas sugestivos de DPOC.

Overed-Sayer C e colaboradores, num estudo *in vitro*, centrado na fibrose pulmonar idiopática (FPI), doença pulmonar crónica e progressiva que apresenta uma elevada morbimortalidade com constantes desafios terapêuticos, encontraram que o nintedanib, uma das raras opções terapêuticas para esta patologia, inibe a sobrevivência e ativação dos mastócitos, proporcionando um mecanismo adicional através do qual este medicamento poderá exercer efeitos anti-fibróticos em doentes com FPI.

Numa comunicação breve, Carreto L, colaborador do Serviço de Pneumologia do Hospital Fernando da Fonseca, integrou uma equipa de investigação que procurou estimar a utilidade de um rastreio regular da deficiência de alfa-1 antitripsina em 1600 doentes do Reino Unido com bronquiectasias, encontrando uma taxa de deteção baixa (0,5%), sugerindo que mais estudos sejam efetuados em populações em diferentes contextos geográficos e/ou genéticos.

Este número inclui ainda breves comunicações de leitura obrigatória no momento atual, nomeadamente sobre a persistência da imunidade em crianças imunizadas com vacina pneumocócica conjugada 13-valente e a evidência de que o isolamento social e a solidão são importantes fatores de risco para admissões hospitalares por doenças respiratórias entre idosos, realçando-se ainda os efeitos nefastos do *vaping* através da discussão de um caso clínico de um jovem de apenas 18 anos.

No comentário final discute-se qual poderá ser a relevância epidemiológica na atual pandemia dos portadores assintomáticos de SARS-CoV-2 ... enfim, boas leituras e muita resiliência!

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ISSN 0003-9888 (print); 1468-2044 (online)

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Patógenos respiratórios e síndrome torácica aguda em crianças com doença falciforme

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/archdischild-2019-317315>).

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Received 27 March 2019

Revised 15 March 2020

Accepted 16 March 2020

Published Online First

8 April 2020



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Para citar: Ploton M-C, Sommet J, Koehl et al. Arch Dis Child 2020;105:891–895.

RESUMO

Contexto As síndromes torácicas agudas (STA) podem estar associadas a infecções das vias respiratórias superiores, mas a epidemiologia dos patógenos respiratórios virais e intracelulares em crianças com doença falciforme (DF) não é conhecida ao pormenor. O objetivo deste estudo foi descrever a epidemiologia dos patógenos respiratórios virais e intracelulares em crianças com DF que apresentem febre e/ou STA.

Materiais e métodos Foi realizado um estudo de coorte, observacional, prospectivo e de centro único com análise hierárquica de casos de controlo em crianças com STA admitidas entre outubro de 2016 e outubro de 2017 com febre e/ou STA na unidade de pediatria do hospital universitário Robert Debré, Paris, França. Foram analisados 20 patógenos respiratórios por PCR *multiplex* na nasofaringe (FilmArray).

Resultados Incluímos 101 crianças. Rácio de sexo M/F de 0,45. A idade média foi de 3,2 anos (IQR: 1,4–8,2). Isolou-se pelo menos um patógeno em 67 doentes (67%). Os vírus mais frequentes foram os seguintes: rinovírus (n=33), adenovírus (n=14), vírus respiratório sincítico (n=13) e vírus parainfluenza (n=11). A infecção por *Mycoplasma pneumoniae* foi detetada num caso. Vinte e três (23%) apresentaram ou desenvolveram STA. Foi realizada uma análise hierárquica de casos de controlo, após emparelhamento de crianças STA e não STA por idade e período de inclusão. Não se observou associação estatística entre qualquer deteção viral ou múltipla infecção viral e STA (p=0,51), embora os vírus de parainfluenza se revelassem duas vezes mais comuns na STA.

Conclusões A deteção viral em crianças febris com DF é frequente, mas a sua associação com a STA não foi demonstrada. Neste estudo, a infecção por *M. pneumoniae* foi rara em crianças jovens com DF a sofrer de STA.

INTRODUCTION

Acute chest syndrome (ACS) is a severe, potentially life-threatening complication of sickle cell disease (SCD), accounting for 9% of all deaths.¹ Pulmonary infection can trigger or complicate ACS.² The most frequent respiratory pathogens in adult patients are intracellular bacteria. *Chlamydia pneumoniae* accounts for 14%–29% of documented infections and *Mycoplasma pneumoniae* for up to 25%.^{1–3} Pyogenic bacteria may be present in 15% of ACS cases in patients with SCD.¹ Because of the high prevalence of infections during ACS and the susceptibility of patients with SCD to infection, international guidelines for ACS recommend systematic antibiotic therapy, active against both pyogenic and intracellular bacteria.^{4,5} Viral respiratory pathogens may be associated with ACS, but their role in triggering ACS remains unclear.^{1–8} Most studies describing pathogens associated with ACS are old. Few of them used respiratory multiplex PCR, and all of them focused on specific pathogens. Paediatric studies are scarce yet given the frequency of viral respiratory infections in children, determining their association with ACS is of interest.

What is already known on this topic?

- Acute chest syndrome (ACS) is a severe complication of sickle cell disease (SCD), accounting for 9% of all deaths.
- Pulmonary infection can trigger or complicate ACS, with intracellular bacteria being the most frequent in adults.
- Viral infections are common in children but their role in triggering ACS remains unclear

What is already known?

- Detection of Respiratory viruses is very frequent in febrile children with SCD.
- There is no significant association between single viral detection, multiple virus infection and onset of ACS.
- Intracellular bacterial detection is rare in young children with ACS.

The main objective of this study was to describe the epidemiology of viral and intracellular respiratory pathogens in children with SCD presenting with fever and/or ACS. Secondary objectives were to assess an association between detection of single, and/or multiple viral infection (MVI) and/or intracellular pathogens with ACS.

PATIENTS AND METHODS

Design

A single-centre, prospective, longitudinal cohort study was conducted from 20 October 2016 to 2 October 2017. Inpatients with SCD, under 18 years of age, hospitalised in the General Paediatric ward of Robert Debré University Hospital, Paris, France, and with fever above 38°C (regardless of apparent cause) and/or with ACS, underwent a nasopharyngeal aspirate. Samples were frozen (–80°C) and a multiplex PCR respiratory panel (FilmArray RP Panel, BioMérieux, BioFire Diagnostics, Salt Lake City, USA) was done, screening for 17 viruses (adenovirus, coronavirus (HKU1, NL63, 229E, OC43), human metapneumovirus, enterovirus/Human Rhinovirus, type A influenza (A, A/H1, A/H1–2009, A/H3), type B influenza, parainfluenza virus (1, 2, 3 and 4), respiratory syncytial virus (RSV)) and three bacterial pathogens (*Bordetella pertussis*, *C. pneumoniae* and *M. pneumoniae*). Each patient could be included several times as long as successive inclusions were separated by at least 4 weeks, to avoid including patients with prolonged viral shedding.

ACS was defined by the presence of a new pulmonary infiltrate involving at least one complete lung segment (consistent with the presence of alveolar consolidation but excluding atelectasis) plus

one of the following: chest pain, temperature of more than 38.5°C, tachypnoea, wheezing or cough.¹ All files of patients with ACS files were reviewed retrospectively by a local SCD expert, blinded to the PCR result, to determine whether ACS was present.

To address the secondary outcomes, a nested case-control analysis was conducted. Patients with ACS were the cases and the controls were non-ACS SCD patients, paired within the cohort according to age (± 14 months) and inclusion period (± 15 days). Antibiotic therapy was administered according to the current French recommendations, that is, an intravenous antipneumococcal antibiotic therapy (either a third-generation cephalosporin or amoxicillin) initiated after bacterial sampling (blood and urine).⁴ In cases of ACS or with chest imaging suggestive of intracellular bacterial pneumonia, a macrolide was added, usually oral azithromycin.

Past history related to SCD, demographics, clinical, laboratory and therapeutic data were collected retrospectively from the patients' files. General information concerning the number of patients with SCD hospitalised during the study period was collected from the hospital administrative records.

Statistical analysis

Anonymised data were collected via an EpiData data entry form and extracted thereafter. Statistical analysis was performed using SAS V.9.4 software. Quantitative data were described using the median (IQR: Q1–Q3). Qualitative data were described using effectives and percentages. To compare included and non-included population Fisher's test for qualitative data and Student's t-test for quantitative data were used. To compare cases and controls and assess factors associated with ACS, logistic conditional regression—adapted to paired data—was used. All statistical tests were two-tailed, and p values of less than 0.05 were deemed statistically significant.

Ethical considerations

The study design was reviewed and accepted by Robert Debré Hospital's local ethical committee IRB n°2016/2962 and data collection was approved by the national informatics and freedoms commission (n°1967433v 0). Parents or legal guardians were informed of the ongoing study via information letters.

RESULTS

General characteristics of the population

In all, 101 patients were included during the study period (figure 1). The sex ratio M/F was 0.45. The median age was 3.2 years (IQR: 1.4–8.2) and the median length of hospital stay was 4 days (IQR: 3–6) ranging from 1 to 23 days. The median delay between fever onset and sampling was 3 days (IQR: 2–5) and the fever lasted 3 days (IQR: 1–4). In all, 17 patients (42 samples) were included repeatedly. Their median age was 2.2 years old (1.3–4.1). In all, 29 of these 42 samples were taken during winter season (September–March). No patient showed successive detection of the same pathogen.

During the study period, 65% of eligible patients (n=183) (among them 21 with ACS) were not included in the study mainly because of the lack of sampling. Their median age was 4.4 year (1.8–11.2) and sex ratio was 0.55 (figure 1). There were no significant differences to included patients concerning age (p=0.1), sex ratio (p=0.08), length of stay (p=0.54) and distribution of hospitalisation causes except for ACS, which was more frequently included (p=0.02). Non-included patients with ACS were significantly older (11.2 year (7.6–13.7) vs 4.2 year (2.3–7.0) p=0.0003) (online supplementary data 1).

Demographics, haematological findings, medical history, clinical and laboratory data at inclusion are shown in table 1. In all, 23 patients presented with or developed ACS (23%). The cause of fever was unknown in four cases. Each patient underwent at least one blood culture. No bacteraemia was found. In all, 100 patients received antibiotic therapy; median duration 11 days (IQR: 8–13), with 84 patients receiving third-generation cephalosporin (4 days, IQR 3–5) followed by amoxicillin. In all, 33 patients (including 19 (57%) from the ACS group)

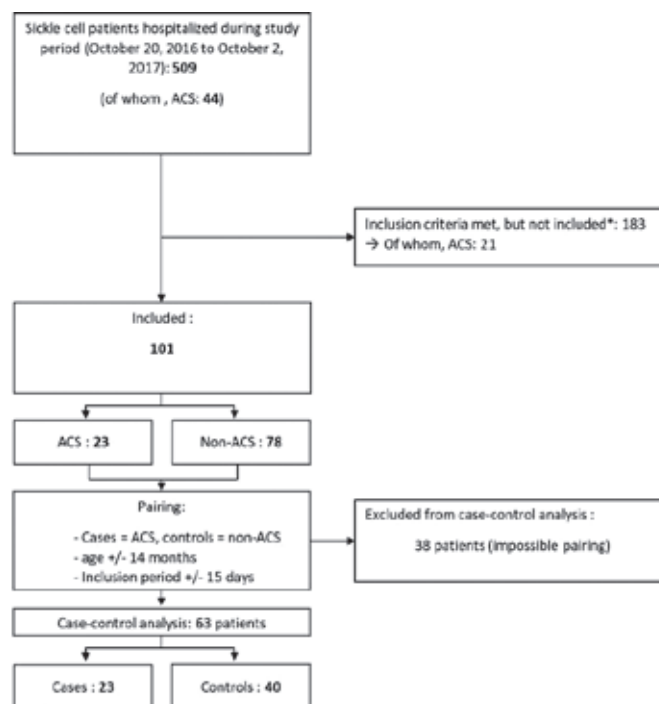


Figure 1 Flow chart of the study ACS, acute chest syndrome. *Lack of sampling.

received macrolides, usually a 3-day course of oral azithromycin. Six patients received oseltamivir.

Nasopharyngeal aspirate multiplex PCR results

In all, 67 patients had a positive Multiplex PCR, 41 with one virus and 26 with two or more. Rhinovirus was the most frequent virus (33 cases), followed by adenovirus (14 cases), RSV (13 cases) and parainfluenza virus (11 cases). Multiplex PCR results are presented in online supplementary data 2.

Among the patients with vaso-occlusive crisis (n=22), 18 had a positive multiplex PCR. Among patients with respiratory symptoms on inclusion (n=45), 37 had a positive PCR. Rhinovirus was most frequently involved in MVI (15 cases), followed by parainfluenza viruses (nine cases). Three patients had 3-virus-MVI. *M. pneumoniae* was positive using multiplex PCR in one patient with ACS (who did not need intensive care unit admission or ventilation). Monthly distribution of viral infections is shown in figure 2.

Case-control analysis

All ACS cases were paired, 17 with a 1:2 case/control ratio and 6 with a 1:1 ratio. The analysis of the case-control population yielded a median age of 5.4 years (IQR: 2.0–11.8). PCR data and comparison between the cases and control on the clinical and laboratory characteristics are shown in table 2.

The C-reactive protein value and neutrophil count were significantly higher in the cases compared with the controls (p=0.01 and p=0.03, respectively). Other variables were not significantly different between the two groups even if clinical history tended to be more severe in the ACS group.

DISCUSSION

Very few studies have assessed the association between viral and intracellular pathogens and ACS in children with SCD.^{6,9} Our study is the largest to date using multiplex PCR detection in nasopharyngeal aspiration. Viral detection in children with ACS and/or fever is frequent (67%) with a predominance of rhinovirus, followed by RSV and adenovirus.

In a previous single-centre prospective study lasting 1 year, multiplex PCR was used to detect respiratory pathogens in 60 children with SCD (including nine with ACS). Viruses were detected in 78% of the patients (rhinovirus: 62%, bocavirus: 26%, influenza: 23%, parainfluenza 23%).⁶ No significant association with ACS was shown, but the statistical power of the study was

Table 1 Demographics, haematological and medical history, clinical and laboratory presentation of children with sickle cell disease and fever

	N (%) median (IQR)
Total/male	101/45
Age (years)	3.2 (1.4–8.2)
Genotype	
SS/ SB ⁰ / SS or SB ⁰ *	91 (90)
SB+/SC	10 (10)
Baseline haemoglobin level (g/L)	
SS, SB ⁰ , SS/SB ⁰ genotype	85 (77–90)
SB+, SC genotype	109 (95–110)
Relevant clinical history	
Associated G6PD deficiency	15 (16)
History of ACS	20 (20)
Repeated VOC (>3 in the previous year)	35 (35)
History of splenectomy	19 (19)
Hydroxyurea treatment†	27 (27)
Iterative transfusion therapy†	13 (13)
History of asthma	26 (26)
Cerebral vasculopathy	12 (13)
Laboratory values (regardless of diagnosis)	
CRP maximum level during febrile episo	73.0 (17.0–160.5)
Procalcitonin maximum level (ng/mL)	0.3 (0.1–0.6)
Leucocytes maximum level (x10 ⁹ /L)	17.9 (13.0–22.3)
Neutrophils maximum level (x10 ⁹ /L)	9.1 (6.1–15.9)
ACs subgroup	n=23 (23)
Age (years)	4.2 (2.3–7.0)
Non-ACs subgroup	n=78 (77)
Age (years)	3.0 (1.4–8.8)
Respiratory symptoms ‡	45 (59)
Discharge diagnosis	
VOC	22 (29)
Acute gastro-enteritis	2 (3)
Upper respiratory tract infection	25 (32)
Lower respiratory tract infection	21 (27)
Parvovirus-related anaemia	4 (6)
Acute splenic sequestration	2 (3)
Malaria	1 (2)

Upper respiratory tract infections were as follows: tonsillitis (six cases), acute otitis media (four cases) and other (15 cases).

Lower respiratory tract infections were as follows: acute bronchiolitis (two cases), documented influenza (specific PCR) (four cases), pneumonia (11 cases) and asthma exacerbation (two cases).

*Genotype uncertain due to absence of genetic study.

†Ongoing on inclusion.

‡Regardless of discharge diagnosis.

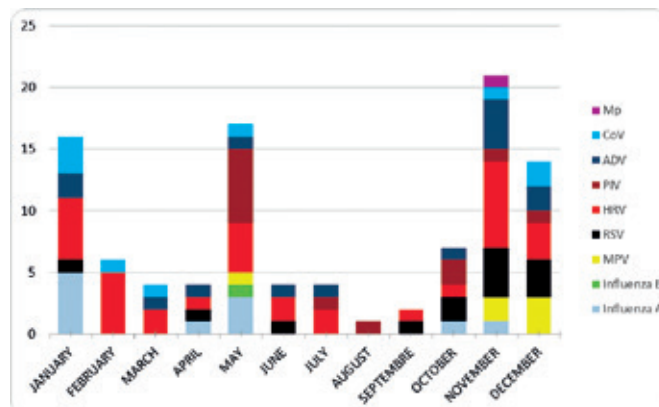
ACS, acute chest syndrome; CRP, C-reactive protein; G6PD, glucose-6-phosphate dehydrogenase; ICU, intensive care unit; VOC, vaso-occlusive crisis.

limited. Another study showed that rhinovirus, adenovirus and bocavirus were the most frequently detected viral pathogens in 20 children with SCD under 5 years of age in Madagascar.⁹ However, in our study, the multiplex PCR was not designed to detect bocavirus infections, limiting the accuracy when comparing our results with these studies.

Our data were also comparable to a geographically and chronologically similar paediatric cohort without underlying disease. Among 381 respiratory viral PCRs done in inpatients with respiratory symptoms (Multiplex PCR FilmArray), 51% were positive (picornaviruses: 52%, RSV: 11%, parainfluenza viruses: 7%). In our study, seasonal distribution was similar to this study.¹⁰

Detection of viral nucleic acid by PCR does not predict clinical presentation. Asymptomatic viral infection or prolonged asymptomatic shedding can occur. Rhinovirus was less strongly associated (1.43 (1.03–1.97)) and adenovirus, coronavirus and bocavirus were not significantly associated with respiratory symptoms.¹¹ Consistently, in our study, nested case–control analysis did not yield any significant association between single viral detection, MVI and onset of ACS after adjusting for age and inclusion period.

Data from the literature are heterogeneous, but influenza and RSV seem frequently involved in ACS. Thus, in children with SCD, influenza-related hospitalisations are 177/100 000 with a hospitalisation risk ratio of 88 (75–104) compared with non-SCD children.⁸

**Figure 2** Monthly distribution of the number of cases by virus type in sickle cell children hospitalised from 20 October 2016 to 2 October 2017. ADV, adenovirus; CoV, coronavirus; HRV, rhinovirus humain; Mp, Mycoplasma pneumoniae; MPV, metapneumovirus; PV, para-influenza virus; RSV, respiratory syncytial virus.

ACS cases were reported after influenza infection (15%–50% of cases depending on the year).^{12–14} These studies did not assess the role of bacterial superinfection in the onset of ACS.

RSV-related hospitalisation rate and clinical presentation in SCD children are described to be comparable to influenzarelated cases, with younger age as the only difference (1.9 vs 4.8 years, $p<0.001$) and ACS onset in 26% of cases.⁷ A retrospective study of 466 SCD children and over 2000 febrile episodes showed that signs of upper respiratory tract infections predicted evolution towards ACS with an OR of 2.1 (95% CI 1.5–2.9).¹⁵ We found only one case of *M. pneumoniae* infection using multiplex PCR, in a child with ACS and no *C. pneumoniae*. The ACS study group isolated *M. pneumoniae* (using PCR or serology) in 20% of documented ACS cases and in 12% of subjects less than 5 years of age.¹⁶ The low number of *M. pneumoniae* in our study can be explained by the young age of included patients, and the shortness of the period of observation (1 year).^{17,18} However, two other studies found very few or no cases of *M. pneumoniae*, over different periods of time and geographical settings.^{6,9}

The performance characteristics of the FilmArray test has been demonstrated.¹⁹ However, sputum has shown greater sensitivity than nasopharyngeal aspiration for *M. pneumoniae* diagnosis.^{20,21} Among the 32 patients who received macrolides, only seven were sampled before antibiotic therapy was started. The median time between starting treatment and sampling was 3.3 days. One paediatric study in patients with non-SCD showed reduction of quantitative PCR after macrolide therapy excluding azithromycin,²² but several other studies found that *M. pneumoniae* qualitative PCR was positive for lengthy periods of time after antibiotic therapy.^{20,23} Thus, we hypothesised that short duration antibiotic administration could not explain the negative findings for all study samples for *M. pneumoniae*.

Our results suggest that the role of intracellular pathogens in young children with ACS could be overestimated and could lead to macrolide overprescription in our population. Thus, the question of *M. pneumoniae* screening before prescribing macrolides should be raised or a prescription of macrolide reserved for clinical presentation suggestive of *Mycoplasma* infection. However, a vast retrospective study (14480 ACS episodes over 31 centres) suggested that adherence to antibiotic-therapy guidelines in ACS was associated with lower readmission rates with an OR of 0.71 (95% CI 0.50–1.00) for ACS-related readmission and of 0.50 (95% CI 0.39–0.64) for all causes of readmission.²⁴

Altogether, the findings of our study show that multiplex PCR detection in naso-pharyngeal aspiration add to the knowledge of respiratory viral infections epidemiology in SCD. The rapid results and the broad spectrum of the multiplex PCR might also improve the practical management of the patients (rapid adaptation of *M. pneumoniae* treatment, use of isolation measures). However, further studies are needed to assess the cost-effectiveness of this procedure.

Table 2 Virus identification data and comparison for clinical and laboratory data between ACS and control children with sickle cell disease

Variable	Controls (n=40) N (%) Med (IQR)	Cases (ACs) (n=23) N (%) Med (IQR)	P value
Male sex	17 (43)	9 (39)	0.94
Genotype			
SS/SB*	34 (85)	22 (96)	0.32
SB+ / SC	6 (15)	1 (4)	
Baseline haemoglobin level (g/L)			
SS, SB*, SS/SB* genotype	81 (75–88)	85 (80–8.7)	0.31
SB+, SC genotype	106 (85–110)	N=0*	N/A
Relevant clinical history			
Associated G6PD deficiency	6 (16)	4 (19)	>0.99
History of ACS	9 (23)	9 (39)	0.35
Repeated VOC (>3 in the previous year)	15 (38)	14 (61)	0.2
History of splenectomy	8 (20)	7 (30)	0.45
Hydroxyurea treatment (ongoing on inclusion)	11 (28)	11 (48)	0.26
Iterative transfusion therapy (ongoing on inclusion)	7 (18)	5 (24)	0.81
History of asthma	13 (33)	7 (30)	0.51
Cerebral vasculopathy	4 (10)	3 (14)	>0.99
Laboratory data			
CRP maximum level (mg/L)	34.4 (11.0–146.0)	189.9 (127.0–244.0)	0.01
Leucocytes maximum level (x10 ⁹ /L)	16.0 (10.7–20.7)	22.3 (15.2–24.8)	0.06
Neutrophils maximum level (x10 ⁹ /L)	7.9 (5.5–12.5)	13.7 (10.5–19.4)	0.03
Multiplex PCR			
Negative	16 (40)	7 (31)	0.51
Positive	24 (60)	15 (65)	
Undetermined	0 (0)	1 (4)	
If positive, number of viruses detected			
One (single virus infection)	17 (71)	10 (67)	0.58
Two or more (multiple virus infection)	7 (29)	5 (33)	
Rhinovirus 1A detection	11 (46)	9 (60)	0.83
Virus type			
Type A influenza	2 (8)	1 (7)*	†
Type B influenza	0 (0)	0 (0)	†
Metapneumovirus	3 (13)	1 (7)	†
Respiratory syncytial virus A	4 (17)	2 (13)	†
Parainfluenza virus	3 (13)	4 (26)‡	†
Type 1	1 (4)	3 (20)	†
Type 2	0 (0)	0 (0)	†
Type 3	2 (8)	0 (0)	†
Type 4	0 (0)	2 (13)	†
Type 3 adenovirus	4 (17)	1 (7)	†
Coronavirus	4 (17)	0 (0)	†
Coronavirus NL63	1 (4)	0 (0)	†
Coronavirus 229	2 (8)	0 (0)	†
Coronavirus OC43	1 (4)	0 (0)	†
Coronavirus HKU1	0 (0)	0 (0)	†
<i>Mycoplasma pneumoniae</i>	0 (0)	1 (7)	†

Chlamydia pneumoniae and *Bordetella pertussis* were not detected.

*One patient tested positive for Type A influenza but result remained equivocal as for subtype.

†Irrelevant statistical testing due to reduced effectiveness.

‡Numbers of patients with different types of each virus does not match with total number due to several cases of co-detection in the same patient.

ACS, acute chest syndrome; CRP, C-reactive protein; G6PD, glucose-6-phosphate dehydrogenase; MD, missing data; p, p value issued from logistic conditional regression taking patient pairing into account; VOC, vaso-occlusive crisis.

Our study has several limitations. First, the low number of patients prevented testing associations between individual viruses and ACS.

Second, many patients meeting the inclusion criteria were not included, although most causes for non-inclusion were random. Thus, the risk of selection bias was low. Moreover, distribution of hospitalisation causes and characteristics of the children were similar between included and non-included patients, except for ACS and lower respiratory tract infection.

Patients with ACS were included more often (p=0.02) as well as lower respiratory tract infection patients (p=0.01). Yet,

nonincluded patients were significantly older. This selection bias should induce viral over-representation in included patients, and in patients with ACS and under-representation of *M. pneumoniae* infection, known to affect older children (see online supplementary data 1).

Third, we did not screen for bacterial causes of lower respiratory tract infection, owing to the invasiveness of lower respiratory sampling. We could therefore not rule out bacterial-viral co-infections. The ACS cases had significantly higher inflammatory markers, suggesting the possibility of bacterial-viral co-infection. Consequently, viral detection should not prevent empiric antibiotic prescription.²⁴ Nevertheless, ACS itself could explain the increase in inflammatory markers.

CONCLUSIONS

Our study confirms high respiratory virus infection and low *M. pneumoniae* prevalence in young febrile, patients with SCD, but no association with ACS. It does not address the association with pyogenic infection; *M. pneumoniae* could be systematically screened before prescribing macrolides, where rapid results are available, to decrease unnecessary prescription and emergence of macrolide resistance.

Contributors M-CP substantially contributed to the conception and design of this article, reviewed the literature, summarised and analysed the literature data and drafted the initial manuscript. She critically reviewed the manuscript for important intellectual content and reviewed and revised the manuscript. JS substantially contributed to the conception and design of this article and data statistical analysis, critically reviewed the manuscript for important intellectual content, and reviewed and revised the manuscript. BK substantially contributed to the conception and design of this article, supported the literature review, critically reviewed the manuscript for important intellectual content, and reviewed and revised the manuscript. JG substantially contributed to the data collection of this article, supported literature review, critically reviewed the manuscript for important intellectual content, and reviewed and revised the manuscript. LH critically reviewed the manuscript for important intellectual content, and reviewed and revised the manuscript. PM-K substantially contributed to the data collection. She critically reviewed the manuscript for important intellectual content, and reviewed and revised the manuscript. MB critically reviewed the manuscript for important intellectual content, and reviewed and revised the manuscript. ELR substantially contributed to the conception and design of this article, supported the literature review, led the data statistical analysis, critically reviewed the manuscript for important intellectual content, and reviewed and revised the manuscript. SB substantially contributed to the conception and design of this article and to the data collection. He critically reviewed the manuscript for important intellectual content, and reviewed and revised the manuscript. AF substantially contributed to the conception and design of this article and to the data collection. He supported the literature review, critically reviewed the manuscript for important intellectual content, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

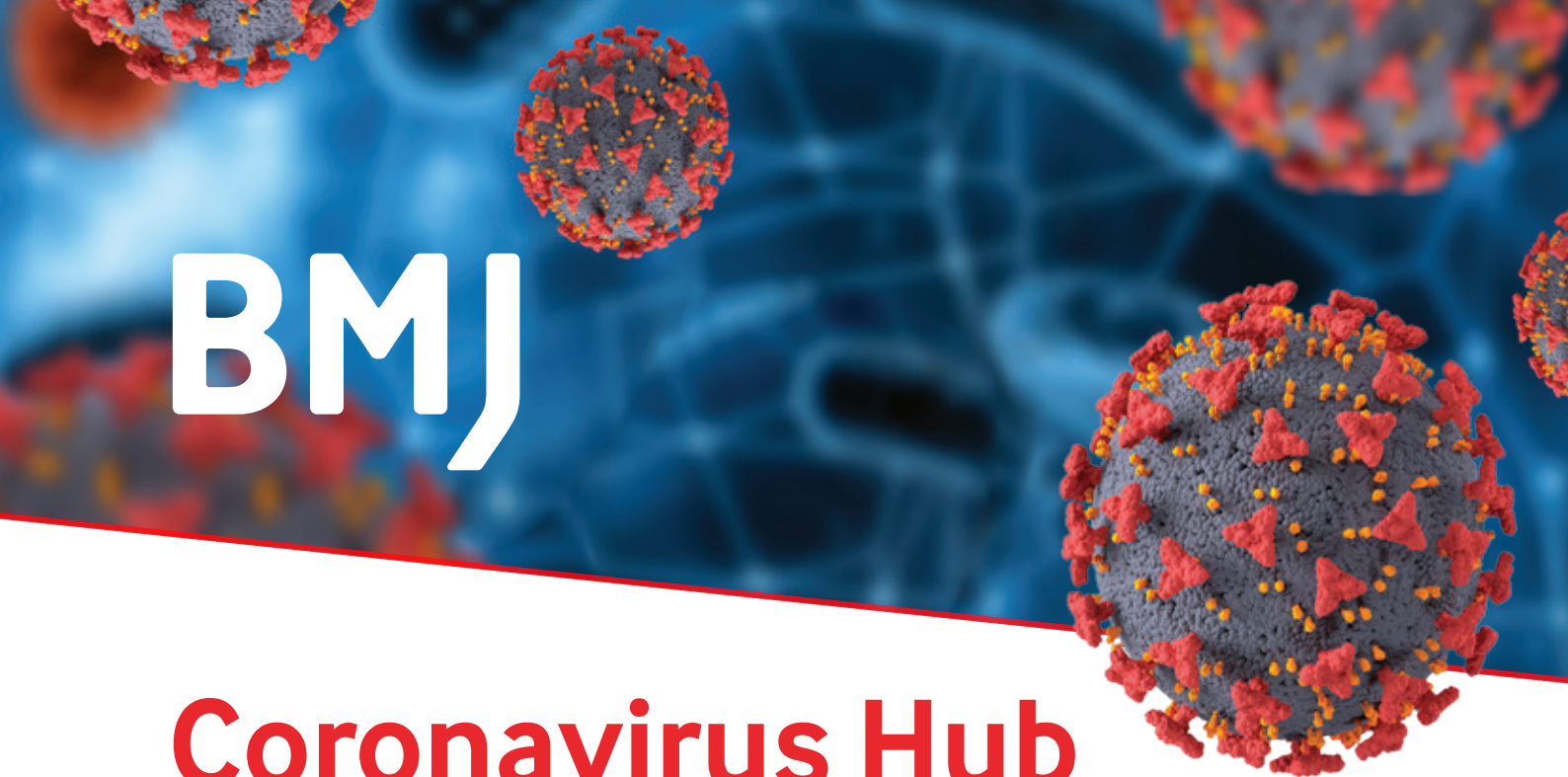
Ethics approval The study design was reviewed and accepted by Robert Debré Hospital's local ethical committee IRB n°2016/2962 and data collection was approved by the national informatics and freedoms commission (n°1 967 433 v 0).

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data are available upon reasonable request. Data are available upon reasonable request made to corresponding author.

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Pulso paradoxal detetado por oximetria prevê gravidade na asma pediátrica

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/archdischild-2019-318043>).

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Received 6 August 2019
Revised 10 January 2020
Accepted 5 February 2020
Published Online First
24 February 2020



► <http://dx.doi.org/10.1136/archdischild-2020-318936>



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Para citar: G Krishnan S, Wong HC, Ganapathy S, et al. Arch Dis Child 2020;105:533–538.

RESUMO

Objetivo Avaliar se a detecção visual qualitativa do pulso paradoxal (PP) no pletismógrafo do oxímetro de pulso consegue prever resultados para crianças com dificuldade respiratória moderada a grave numa unidade de urgência pediátrica.

Desenho Estudo de coorte prospectivo.

Enquadramento Unidade de Urgência Pediátrica de um hospital pediátrico terciário em Singapura.

Doentes Crianças tratadas para pieira moderada a grave na sala de reanimação da unidade de urgência.

Intervenções Os doentes foram avaliados quanto à presença de PP com base na detecção visual do pletismógrafo do oxímetro antes e depois de terapia inicial com inalação de broncodilatador.

Principais medidas de resultados Estas incluem a necessidade de medicamentos adjuvantes, tais como aminofilina ou sulfato de magnésio, a necessidade de ventilação suplementar e a necessidade de admissão na unidade de alta dependência (UAD) ou unidade de cuidados intensivos (UCI).

Resultados O estudo incluiu 285 doentes, dos quais 78 (27,4%) apresentavam PP nas Urgências. 40 (14,0%) apresentaram PP após o tratamento inicial. As crianças com PP após o tratamento inicial apresentaram riscos relativos significativos (RR) de necessidade de medicação adjuvante (RR 12,5, 95% IC 4,0 a 38,6), necessidade de ventilação suplementar (RR 5,6, 95% IC 1,2 a 26,5) e admissão na UAD/UCI (RR 5,6, 95% IC 3,0 a 10,4).

Conclusão A detecção qualitativa de PP na oximetria de pulso pode ser utilizada como uma ferramenta potencial no local de atendimento como apoio à avaliação da resposta ao tratamento inicial em doentes pediátricos com agudizações moderadas a graves de asma. No futuro, são necessários estudos para avaliar e validar o seu papel na orientação do tratamento da asma pediátrica aguda em unidade de urgência.

INTRODUCTION

Asthma is one of the most common reasons for paediatric emergency department (ED) visits.¹ The severity of asthma exacerbations is often assessed based on subjective clinical indicators. Asthma severity scores such as the Pediatric Respiratory Assessment Measure² and the Pediatric Asthma Severity Score (PASS)³ have been shown to be valid in gauging the severity of an exacerbation. Although interobserver reliability has been shown with these scoring tools, they too involve subjective clinical assessment.

International guidelines state that peak expiratory flow rate (PEFR) is a more valid measure of airway obstruction. However, PEFR is difficult to obtain in an acute setting or in children

What is already known on this topic?

- Asthma is one of the most common reasons for attendance to the paediatric emergency department (ED).
- There is a need for ED physicians to efficiently manage these patients and for accurate allocation of appropriate resources.
- Studies have shown the quantitative assessment of oximeter plethysmograph variability, as a surrogate for pulsus paradoxus (PP), can be used to assess severity of asthma

What is already known?

- First study to use qualitative assessment of plethysmograph variability on non-specialised, bedside physiological monitors to detect presence of PP to prognosticate moderate to severe acute asthma exacerbation in children.
- Presence of PP at ED presentation has good correlations with acute clinical severity using Pediatric Asthma Severity Score.
- Presence of PP after initial inhaled bronchodilator therapy has a higher relative risk for needing adjunct medications (aminophylline/ magnesium sulfate) and for needing admission to high dependency and intensive care units

younger than⁵ years who may be too ill or too young to perform the test accurately. There are few other objective measures to assess the severity of asthma.⁴

Pulsus paradoxus (PP) is an objective bedside measurement for assessment of airway obstruction and response to treatment. Adolf Kussmaul first defined PP in 18735 as a decrease in systolic blood pressure of more than 10 mm Hg during inspiration. Patients with obstructive airway disease have a loaded inspiration due to difficulty in exhalation, causing a fall in intrathoracic pressure, which causes an increase in right ventricular diastolic volume and stroke volume.⁶ During expiration, the left ventricular diastolic volume and stroke volume increase while the

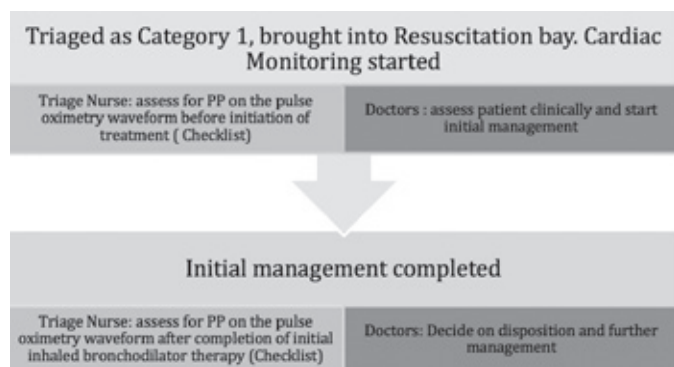


Figure 1 Sequence of assessment for PP on pulse oximetry. PP, pulsus paradoxus.

right ventricular volumes return to baseline values. This causes variability of the systolic blood pressure during inspiration and expiration.^{7 8}

PP is traditionally measured using a sphygmomanometer or intra-arterial catheter,⁹ both of which are infrequently used in the ED. Pulse oximeters give a qualitative display of the pulse amplitude of the vascular bed underlying the probe.¹⁰ Recent studies demonstrated that such plethysmograph waveforms accurately represent the peripheral arterial waveform and can be used to estimate the degree of PP where a greater degree of PP correlates with higher asthma severity.

The aim of this study is to investigate if qualitative visual detection of PP on the pulse oximeter plethysmograph (which is based on a regular respiratory variation in the amplitude of the waveform) can be used to predict outcomes for children attending the ED) with moderate to severe respiratory distress. We excluded children with mild wheeze as clinical evaluation is sufficient, and additional assessment or prognostic tools are unlikely to provide further clinical utility.

METHODOLOGY

Patients

This is a single-centre study conducted prospectively in the ED of a tertiary care children's hospital from December 2014 to May 2015. We included children aged up to 16 years who attended the ED with moderate to severe respiratory distress and who were triaged as category 1. Patients less than 24 months of age with no history of recurrent wheeze or asthma and those with the diagnoses of pleural effusions, croup, anterior mediastinal tumours and anaphylaxis were excluded. Patients were also excluded if they could not be assessed for PP before starting treatment.

Study design

Patients presenting to the ED were first triaged by nurses according to the Singapore Paediatric Triage Scale (online supplementary appendix 1). Patients with respiratory distress and who needed to be seen with immediate priority were triaged as category 1 as per the department's triage guidelines (online supplementary appendix 2). They were brought into the resuscitation bay and put on cardiorespiratory monitoring (Phillips Intellivue MP30 cardiac monitor). The triage nurse immediately assessed the pulse oximeter plethysmographic waveform on the cardiac monitor to detect the presence of PP (figure 1). This was documented on a PP data sheet.

The patient was then managed by a team of ED physicians according to the clinical severity of respiratory distress.

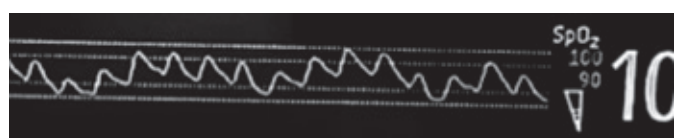


Figure 2 Plethysmographic variability in a child with pulsus paradoxus.

Management was standardised according to the department's guidelines (online supplementary appendix 3). Initial resuscitative management included bronchodilators (inhaled Salbutamol and Ipratropium bromide) administered through a metered dose inhaler or nebuliser, and oral or intravenous steroids. Adjunct medications such as intravenous magnesium sulfate or aminophylline were administered for refractory respiratory distress or status asthmaticus after initial inhaled bronchodilator therapy.

After the initial set of two to three cycles of intensive inhaled bronchodilator therapy, the same triage nurse again assessed the pulse oximeter plethysmographic waveform for PP and documented it on the PP datasheet. This datasheet was collected at the end of the treatment and analysed.

During the entire resuscitation, the ED physicians were not aware of the data or documentation of PP so as not to alter the patient assessment or management. Within 2 hours of triage, the physicians would make a decision on the disposition of the child from the ED based on the patient's clinical severity and the level of further treatment required.

Determination of pulsus paradoxus

PP was taken to be qualitatively present if there was a regular variation in the amplitude of the plethysmographic waveform in accordance with the respiratory cycle of the patient (figure 2).

Triage nurses were trained to detect PP on the waveform (online supplementary appendix 4). By the time the study commenced, the triage nurses were confident and consistent in their assessments of the pulse oximeter plethysmograph.

Doctors in the department were aware of the ongoing study but were not trained in the evaluation of the pulse oximetry detection of PP. The teaching sessions on recognising PP on pulse oximetry included only the nurses. In our department, it is not part of our assessment tools to use PP as a measure of our asthma assessment and therefore our asthma management guidelines do not depend on the presence of PP.

Outcomes measured

The primary outcomes measured include the need for adjunct medications such as aminophylline or magnesium sulfate, the need for supplementary ventilation such as non-invasive positive pressure ventilation (continuous/bilevel positive airway pressure) or endotracheal intubation, and the need for admission to the high dependency unit (HDU) or intensive care unit (ICU). The outcomes were compared for those with PP at arrival at the ED and those with PP after initial inhaled bronchodilator therapy.

Data collection and statistical analysis

Data were reviewed from electronic medical records as well as from the PP data sheets, which were filled by triage nurses and deposited into a collection box.

Fisher's exact probability test was used to see whether there were significant differences between the PP group and those without PP at ED presentation prior to treatment in terms of demographics, the patients' history of wheezing, the patients' history of admission to high dependency or ICU and the patients' history of use of preventers. Mann-Whitney U test was performed to see whether there were significant differences in age and PASS between those with PP and those without PP at ED presentation. Fisher's exact probability test was carried out to see whether there were significant statistical differences in tachypnoea (based on age), oxygen saturation, use of adjuncts, need for supplementary ventilation (non-invasive ventilation or endotracheal intubation) and need for high dependency or ICU care between the PP group and those without PP at ED presentation, and whether there were significant statistical differences in the use of adjuncts, the need for supplementary ventilation and the need for high depen-

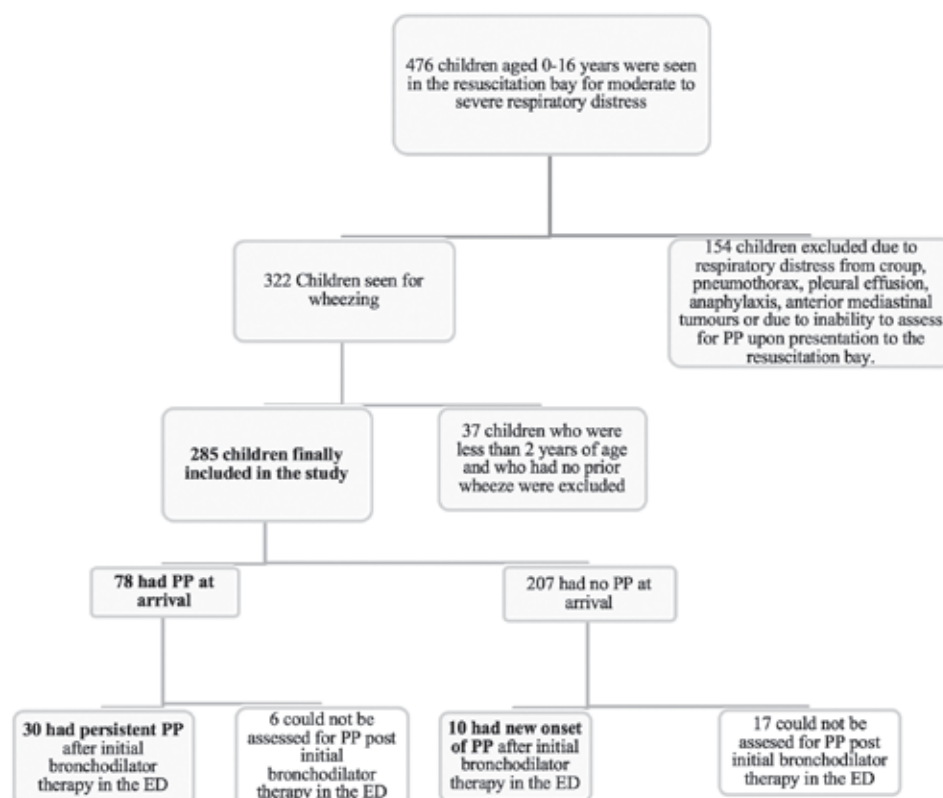


Figure 3 Flowchart of patients included in study. ED, emergency department; PP, pulsus paradoxus.

dency or ICU care between the PP group and those without PP after initial management. Statistical significance was set at 5%. Statistical analyses were performed using IBM SPSS Statistics V.25 (IBM, Armonk, New York, USA).

RESULTS

A total of 476 patients were seen for moderate to severe respiratory distress in the resuscitation bay of our ED during the study period. Of these, 37 patients were excluded for being less than 24 months of age and with first presentation of wheeze and 154 patients were excluded from the analysis for having respiratory distress due to croup, pneumothorax, pleural effusion, anaphylaxis, anterior mediastinal tumours or due to inability to assess for PP at arrival (figure 3). Of the remaining 285 patients who were included in the study, 78 (27.4%) were assessed to have PP at arrival. There were no significant differences between the PP group and those without PP at arrival in terms of demographics and the patients' wheezing histories (table 1). Study participants were primarily in early childhood and mainly of Chinese race. There was also no significant difference in the degree of hypoxia but patients with PP at arrival were significantly found to have higher PASS (table 2). PP at arrival was significantly associated with more severe asthma with PASS of 4–6, $p<0.001$ (table 3).

Patients who presented with PP at arrival were found to have higher relative risk (RR) of requiring adjunct medications such as aminophylline and magnesium sulfate (RR 3.0, 95% CI 1.1 to 8.1; $p=0.033$) and admission to HDU/ICU (RR 2.1, 95% CI 1.1 to 3.9; $p=0.025$) (table 4). However, there was no significant difference in the requirement for supplementary ventilation ($p=0.351$).

There were 23 patients with unavailable information on PP after initial bronchodilator therapy in the ED. Of the remaining 262 patients, 30 (41.7%) of the patients who presented with initial PP had persistence of PP after initial bronchodilator therapy in the ED, while 10 patients (5.3%) who did not have PP initially were assessed to have PP after initial bronchodilator therapy. These 40 patients who had PP after initial bronchodilator the-

Table 1 Demographics of patients presenting to ED with moderate to severe wheezing

Variables	PP present at arrival in ED (n=78)	PP absent at arrival in ED (n=207)	P value
Median age (25th–75th percentile)	3.86 (2.45–5.38)	3.55 (2.18–5.89)	0,535
Age			
Number of children <1 year of age	3 (3.8%)	15 (7.2%)	0,637
Number of children 1–2 years old	9 (11.5%)	26 (12.6%)	
Number of children >2 years old	66 (84.6%)	166 (80.2%)	
Race			
Chinese	33 (42.3%)	91 (44.0%)	0,728
Malay	28 (35.9%)	82 (39.6%)	
Indian	11 (14.1%)	22 (10.6%)	
Others	6 (7.7%)	12 (5.8%)	
Gender			
Male	46 (59.0%)	114 (55.1%)	0,594
History of previous admission to HDU or ICU	9 (11.5%)	16 (7.7%)	0,349
History of use of preventers (inhaled corticosteroids or montelukast)	9 (11.5%)	47 (22.7%)	0,044
Details of pretreatment received prior to ED attendance			
No pretreatment	33 (42.3%)	104 (50.2%)	0,496
Inhaled Salbutamol given via MDI space chamber	36 (46.2%)	83 (40.1%)	
Nebulised bronchodilators	9 (11.5%)	20 (9.7%)	

P value of less than 0.05 is considered significant.

ED, emergency department; HDU, high dependency unit; ICU, intensive care unit; MDI, metered dose inhaler; PP, pulsus paradoxus.

rapy were found to have a significantly greater risk of requiring adjunct medications (RR 12.5, 95% CI 4.0 to 38.6; $p<0.001$), need for supplementary ventilation (RR 5.6, 95% CI 1.2 to 26.5; $p=0.048$) and admission to the HDU/ICU (RR 5.6, 95% CI 3.0 to 10.4; $p<0.001$) (table 5).

DISCUSSION

Our study showed that children with PP, before and after initial inhaled bronchodilator therapy had a higher risk of requiring adjunct medications and admission to HDU/ICU.

Many studies have successfully demonstrated the phenomenon of PP in patients with severe airways obstruction.^{6,11,12}

Table 2 Respiratory status on presentation to the ED

	PP present (n=78)	PP absent (n=207)	P value
Tachypnoea present	76 (97.4%)	201 (97.1%)	1
Oxygen saturation			
≥95%	29 (37.2%)	78 (37.7%)	0.274
92%–94%	36 (46.1%)	78 (37.7%)	
<92%	13 (16.7%)	51 (24.6%)	
Median (IQR) PASS*	5.00 (4.00–5.00)	3.00 (3.00–5.00)	<0.001

P value of less than 0.05 is considered significant.

*PASS scoring includes wheeze, work of breathing and prolonged expiratory phase.

ED, emergency department; PASS, Pediatric Asthma Severity Score; PP, pulsus paradoxus.

Recently, studies have shown correlations between the quantitative variability in pulse oximeter plethysmograph and PP measured via traditional methods of sphygmomanometer and intra-arterial blood pressure monitoring.⁹ For example, Wright et al compared finger arterial pressure monitors to the patient's respiratory cycles to determine the high and low blood pressure measurements during that time frame.¹³ Hartet et al measured respiratory waveform variations precisely in millimetres in patients requiring mechanical ventilation and correlated this with PP.¹⁴ On the other hand, Arnold et al estimated PP by calculating the area under the curve of a plethysmograph tracing and compared this with FEV.¹⁵ These different methods have successfully shown correlations between PP detected by pulse oximetry and existing criterion standards.

However, these methods are challenging to use in a time-critical setting such as the ED. To our knowledge, the use of qualitative detection of PP to predict outcomes has not been investigated before. Our study is the first of its kind in showing that simple pattern recognition of PP on pulse oximeter plethysmograph can be used to predict outcomes and hence guide management of children with moderate to severe respiratory distress. Brandwein *et al*¹⁶ found a significant difference in the degree of PP between children discharged home versus children admitted to the hospital. They studied the Pleth Variability Index, which is a ratio of the calculated difference in maximum and minimum amplitude of the plethysmograph waveform and the maximum amplitude.¹⁶ Though our study did not evaluate the exact degree of PP, we had similar findings of a higher RR of getting admitted to HDU/ICU among those detected to have PP on the plethysmograph after initial management. This shows that even without assessing the exact degree of PP, outcomes may be predicted on qualitative visual assessment of PP and it is an easy point-of-care assessment technique which does not involve additional special equipment and can be performed by anyone trained to recognise patterns. It can also be a useful and objective prognosticating tool, which can be easily performed even in children younger than 5 years or those who are too ill to comply with spirometry.

Different studies have measured the PP on plethysmography at different time points. In particular, Wright et al compared the degree of PP at three time points: before initiation of treatment, at 30 min and at 60 min after treatment. Their study found that the PP was significantly higher for the poor

outcome groups compared with good outcome groups at all measurement times.¹³

In our study, we found that while the need for adjunct medications and the need for admission to HDU/ICU were higher in both the PP groups before and after initial management, the RR for these outcomes was much higher in the group with persistent PP after initial bronchodilator therapy. This could be attributed to the presence of persistent severe asthma and bronchospasm that is refractory to initial management, which creates a greater need for adjunct medications and for closer monitoring in HDU/ICU, whereas those who show resolution of PP could have had a reversal of bronchospasm with initial management and therefore have a lower risk for requiring HDU/ICU admission. We acknowledge the limitations given the low frequencies of these clinical outcomes.

In our study, we found that those with PP at arrival had higher PASS than those without. Although interobserver reliability has been shown with using PASS, there is a certain degree of subjectivity in its assessment. Assessment of PP on plethysmograph can be easily done using non-specialised besides physiological monitors and provide an additional tool when assessing children with moderate to severe asthma.

There are areas for improvement in our study. In our study, only one triage nurse assesses PP on pulse oximetry. This can give rise to interobserver variability. Though we tried to mitigate this limitation through adequate training and testing of the triage nurses, it would still be useful to get two nurses in future studies to improve reproducibility and limit potential variability.

In addition, another limitation is the risk of observer bias as the doctors in the department were aware of the ongoing study and complete blinding of the physicians was not feasible. We attempted to mitigate the observer bias by training only the nurses (and not the doctors) on the detection of PP on pulse oximetry. However, it would be worthwhile to consider doing a similar study in a multicentre trial with blinding of the physicians to assess interobserver variability and to assess the outcomes of children with severe wheezing.

Despite our findings, it is important to note that detection of PP on plethysmography should not replace clinical judgement. Nevertheless, after initial bronchodilator therapy, if PP is still noted on the plethysmography, it may be used as an additional clinical adjunct in the evaluation of the severity of wheeze and guide further management in refractory cases of bronchospasms and status asthmaticus.

CONCLUSIONS

Qualitative detection of PP on pulse oximetry can be used as a potential point-of-care tool to help in the assessment of response to initial treatment in paediatric patients with acute moderate to severe asthma exacerbations. Future studies are needed to assess and validate its role in guiding ED management of acute paediatric asthma.

Table 3 Relative risks (95% CI) of any hypertension and BP non-dipping at 10 year follow-up by OSA status at baseline

Severity (PASS*)	PP present (n=78)	PP absent (n=207)	P value	PPV (%) (95% CI)	NPV (%) (95% CI)	LR+ (95% CI)	LR- (95% CI)
Mild (0)	0	0	<0.001	87.2 (77.7 to 93.7)	57.5 (50.4 to 64.3)	87.2 (77.7 to 93.7)	0.6 (0.5 to 0.7)
Moderate (1–3)	10 (12.8%)	119 (57.5%)					
Severe (4–6)	68 (87.2%)	88 (42.5%)					

P value of less than 0.05 is considered significant.

*PASS scoring includes wheeze, work of breathing and prolonged expiratory phase.

LR+, positive likelihood ratio; LR-, negative likelihood ratio; NPV, negative predictive value; PASS, Pediatric Asthma Severity Score; PP, pulsus paradoxus; PPV, positive predictive value.

Table 4 Associations of oximetry-detected PP, at ED presentation, with primary outcomes

Severity (PASS*)	PP present (n=78)	PP absent (n=207)	Relative risk (95% CI)	P value
Use of adjuncts (intravenous MgSO ₄ , aminophylline)	8 (10.3%)	7 (3.4%)	3.0 (1.1 to 8.1)	0,033
Need for supplementary ventilation (non-invasive or endotracheal intubation)	3 (3.8%)	3 (1.4%)	2.7 (0.6 to 12.9)	0,351
Need for HDU or ICU care	15 (19.2%)	19 (9.2%)	2.1 (1.1 to 3.9)	0,025

P value of less than 0.05 is considered significant.

ED, emergency department; HDU, high dependency unit; ICU, intensive care unit; MgSO₄, magnesium sulfate; PP, pulsus paradoxus.

Table 5 Associations of oximetry-detected PP, after initial inhaled bronchodilator therapy, with primary outcomes

Severity (PASS*)	PP present (n=78)	PP absent (n=207)	Relative risk (95% CI)	P value
Use of adjuncts (intravenous MgSO ₄ , aminophylline)	9 (22.5%)	4 (1.8%)	12.5 (4.0 to 38.6)	<0,001
Need for supplementary ventilation (non-invasive or endotracheal intubation)	3 (7.5%)	3 (1.4%)	5.6 (1.2 to 26.5)	0,048
Need for HDU or ICU care	15 (37.5%)	15 (6.8%)	5.6 (3.0 to 10.4)	<0,001

P value of less than 0.05 is considered significant.

*23 patients could not be assessed for presence of pulsus paradoxus after initial inhaled bronchodilator therapy.

HDU, high dependency unit; ICU, intensive care unit; MgSO₄, magnesium sulfate; PP, pulsus paradoxus.

Acknowledgements We would like to acknowledge the triage nurses at the department of emergency medicine in KK Women's and Children's Hospital, Singapore for their contribution in filling up the pulsus paradoxus data collection sheet before and after initial bronchodilator therapy for each study participant.

Contributors SGK contributed substantially in the methodological design, collecting the data, interpretation of the data, drafting the work and agreeing 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. She approves of the final version to be published. HCW helped in analysis and interpretation of data for the work, revising the work critically for important intellectual content and in approving the final version to be published. She agrees 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. She approves of the final version to be published. SG contributed substantially in the methodological design, collecting the data, interpretation of the data, the analysis and interpretation of data for the work, revising the manuscript critically for important intellectual content and in approval of the final version to be published. He agrees 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. He approves of the final version to be published. GY-KO conceived the presented idea, substantially contributed to the methodological design, analysis and interpretation of data for the work, revising the manuscript critically for important intellectual content and in approval of the final version to be published. He agrees 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. He approves of the final version to be published.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Approval was obtained from the local SingHealth Centralised Institutional Review Board (CIRB) prior to commencement of the study. The CIRB approval number is 2014/091/E.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data are available on reasonable request. The corresponding author (Sandhya G Krishnan, sandhya.krishnan@mohh.com.sg) has stored the deidentified patient data in a password-locked desktop computer and can provide the data on request.

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1 VEZ DIA¹

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breezhaler[®]

Indacaterol/glicopirrônio pó para inalação, cápsulas

Primeira associação fixa LAMA/LABA^{1*}MELHORA OS SINTOMAS DE HOJE^{3**}... REDUZ FUTURAS EXACERBAÇÕES^{2,5#}Estudo CRYSTAL³

117%

Melhoria da dispneia
vs LABA/ICS³(Medida através do TDI.
Cálculo realizado a partir dos dados
de Melhoria do TDI do Estudo
CRYSTAL ($\Delta = 1,10$ uds;
 $p < 0,0001$ às 12 semanas)

17%

de diminuição
na taxa de exacerbações
moderadas a gravesvs SFC²
(às 52 semanas) $p < 0,001$ Estudo FLAME²

**BREEZHALER, O DISPOSITIVO
COM MENOR TAXA DE ERROS CRÍTICOS**
ASSOCIADOS AO SEU USO^{4§}**

*Informação sobre medicamentos do INFARMED consultada em página da internet do site do Infomed (acessada em 2020/01/15); ¹Indacaterol/glicopirrônio(110/50µg 1x dia) vs Salmeterol/Fluticasona(500/50µg 2x dia), glicopirrônio(50µg 1x dia) e tiotropio(18µg 1x dia); ²Melhoria da dispneia vs LABA/ICS³, LABA e LAMA avaliada através do TDI; ³Breezhaler vs restantes inaladores em estudo (Respimat[®], pMDI[®], Turbuhaler[®], Handihaler[®] e Diskus[®]); ⁴Erro crítico: aquele que pode afetar substancialmente a dose que chega ao pulmão; ⁵LAMA: Antagonista muscarínico de longa duração de ação; ⁶LABA: agonista β2 de longa ação; ⁷ICS: Corticosteroide Inalado; ⁸pMDI: inaladores pressurizados doseáveis; ⁹TDI: Transition Dyspnea Index; ¹⁰SFC: Salmeterol/Fluticasona 50/50µg 2x dia; ¹¹Δ: diferença entre terapêuticas. 1. RCM XOTERNA[®] BREEZHALER[®] 05/2019; 2. Wedzicha JA, Banerji D, Chapman KR. Indacaterol/Glycopyrronium Versus Salmeterol/Fluticasone for COPD Exacerbations. New England Journal of Medicine. 2016;374:2222-2234; 3. Vogelmeier CF, Gaga M, Alamian-Mattheis M, Greulich T, Marin JM, Castellani W, et al. Efficacy and safety of direct switch to indacaterol/glycopyrronium in patients with moderate COPD: the CRYSTAL open-label randomised trial. Respir Res. 2017 Jul 18;18(1):140; 4. Molimard M, Raherson C, Lignot S, et al. Chronic obstructive pulmonary disease exacerbation and inhaler device handling: real-life assessment of 2935 patients. Eur Respir J 2017; 49:1601794; 5. Wedzicha JA, Drecomer M, Ficker JH, et al. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): randomised, double-blind, parallel-group study. Lancet Respir Med. 2013;1:199-209; ⁶População estudo FLAME: Doentes com história de ≥1 exacerbações no ano prévio à inclusão; ⁷População estudo CRYSTAL: Doentes com Doença Pulmonar Obstrutiva Crônica moderada e com ≤1 exacerbação no ano prévio; ⁸População estudo FLAME: Doentes com história de ≥1 exacerbações no ano prévio à inclusão.

Xoterna Breezhaler 85 microgramas/43 microgramas, pó para inalação, cápsulas (indacaterol/glicopirrônio) **Nota Importante:** Antes de prescrever consulte o Resumo das Características do Medicamento. **APRESENTAÇÃO:** Pó para inalação, cápsulas contendo 143 microgramas de maleato de indacaterol equivalente a 110 microgramas de indacaterol e 63 microgramas de brometo de glicopirrônio equivalente a 50 microgramas de glicopirrônio. Cada dose libertada (a dose libertada do aplicador bucal do inalador) contém 110 microgramas de maleato de indacaterol equivalente a 85 microgramas de indacaterol e 54 microgramas de brometo de glicopirrônio equivalente a 43 microgramas de glicopirrônio. **INDICAÇÕES:** Xoterna Breezhaler é indicado como tratamento broncodilatador de manutenção para alívio dos sintomas em doentes adultos com doença pulmonar obstrutiva crônica (DPOC). **POSOLOGIA E MODO DE ADMINISTRAÇÃO:** **Adultos:** A dose recomendada é a inalação do conteúdo de uma cápsula uma vez por dia, usando o inalador Xoterna Breezhaler. Deve ser utilizado o inalador fornecido com cada nova prescrição. **Populações especiais de doentes:** **Compromisso renal:** pode ser usado na dose recomendada em doentes com compromisso renal ligeiro a moderado. Em doentes com compromisso renal grave ou com doença renal terminal que necessitem de diálise, este deve ser usado se o benefício esperado superar o risco potencial. **Compromisso hepático:** pode ser utilizado na dose recomendada em doentes com compromisso hepático ligeiro a moderado. Não estão disponíveis dados para a utilização em doentes com compromisso grave da função hepática. **População idosa:** pode ser utilizado na dose recomendada em doentes idosos (idade igual ou superior a 75 anos). **População pediátrica** (<18 anos): a segurança e eficácia não foram estabelecidas. Não existem dados disponíveis. **Modo de administração:** As cápsulas de Xoterna Breezhaler devem ser administradas pela via inalatória oral e apenas com a utilização do inalador Xoterna Breezhaler. As cápsulas não devem ser engolidas. Xoterna Breezhaler deve ser administrado à mesma hora do dia todos os dias. Se for omitida uma dose, esta deve ser tomada assim que possível no mesmo dia. Os doentes devem ser instruídos a não tomarem mais do que uma dose por dia. As cápsulas devem ser sempre conservadas no blister de origem para proteger da humidade, e apenas retiradas imediatamente antes da utilização. Os doentes devem ser instruídos sobre como administrar o medicamento corretamente. Os doentes que não sentirem melhorias na respiração devem ser questionados se estão a engolir o medicamento em vez de o inalar. **CONTRAINDICAÇÕES:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes de Xoterna Breezhaler. **ADVERTÊNCIAS/PRECAUÇÕES:** **♦ Xoterna Breezhaler não deve ser administrado concomitantemente com medicamentos contendo agonistas beta-adrenérgicos de longa duração ou antagonistas muscarínicos de longa duração** **♦ asma:** não deve ser usado no tratamento da asma, os agonistas beta-adrenérgicos de longa duração podem aumentar o risco de acontecimentos adversos graves relacionados com a asma, incluindo mortes relacionadas com a asma, quando utilizados no tratamento da asma **♦ utilização aguda:** não está indicado para o tratamento de episódios agudos de broncospasma **♦ hipersensibilidade:** se ocorrerem reações de hipersensibilidade, em particular angioedema, urticária ou erupção cutânea, o tratamento com Xoterna Breezhaler deve ser descontinuado e deverá ser instituída terapêutica alternativa **♦ broncospasma paradoxal:** administração de Xoterna Breezhaler pode resultar em broncospasma paradoxal, o que pode pôr em risco a vida. Se tal ocorrer, o tratamento deve ser interrompido imediatamente e deverá ser instituída terapêutica alternativa **♦ efeitos anticolinérgicos relacionados com glicopirrônio:** utilizar com precaução em doentes com glaucoma de ângulo estreito e retenção urinária **♦ efeitos sistémicos de beta-agonistas:** tal como com outros agonistas beta-adrenérgicos, deve ser utilizado com precaução em doentes com perturbações cardiovasculares (doença arterial coronária, enfarte agudo do miocárdio, arritmias cardíacas, hipertensão); em doentes com perturbações convulsivas ou tirotóxicose, e em doentes com resposta aumentada aos agonistas beta-adrenérgicos **♦ doentes com compromisso renal grave:** apenas deve ser utilizado se o benefício esperado superar o risco potencial em doentes com compromisso renal grave, incluindo os com doença renal terminal necessitando de diálise **♦ efeitos cardiovasculares de beta-agonistas:** tal como com outros agonistas beta-adrenérgicos, pode causar efeitos cardiovasculares clinicamente significativos em alguns doentes, evidenciados pelo aumento da frequência cardíaca, pressão arterial e/ou sintomas, alterações no eletrocardiograma (ECG) **♦ hipocalcémia:** os agonistas beta-adrenérgicos podem produzir hipocalcémia significativa em alguns doentes, o que potencialmente pode levar a reações adversas cardiovasculares. A diminuição do potássio sérico é usualmente transitória, não requerendo suplementação. Em doentes com DPOC grave, a hipocalcémia pode ser potenciada pela hipoxia e pela terapêutica concomitante, o que pode aumentar a suscetibilidade a arritmias cardíacas **♦ hiperglicémia:** A inalação de doses elevadas de agonistas beta-adrenérgicos pode produzir aumento da glicose plasmática. Ao iniciar o tratamento com Xoterna Breezhaler, a glicose plasmática deve ser monitorizada cuidadosamente em doentes diabéticos. Xoterna Breezhaler não foi estudado em doentes com diabetes mellitus inadequadamente controlada, portanto, é recomendada precaução e monitorização apropriada nestes doentes. **♦ Xoterna Breezhaler contém lactose.** Doentes com problemas hereditários raros de intolerância à galactose, deficiência total de lactase ou má absorção de glicose-galactose não devem tomar este medicamento. **GRAVIDEZ:** apenas deve ser usado durante a gravidez se os benefícios esperados para o doente compensarem os potenciais riscos para o feto. **TRABALHO DE PARTO: Informação relacionada com indacaterol** – tal como com outros medicamentos contendo agonistas beta-adrenérgicos, Xoterna Breezhaler pode inibir o trabalho de parto devido ao efeito relaxante no músculo liso uterino. **ALEITAMENTO:** apenas deve ser considerado se os benefícios esperados para a mulher compensarem qualquer potencial risco para a criança. **FERTILIDADE:** os estudos de reprodução e outros dados em animais não levantam preocupações no que respeita a fertilidade quer em machos quer em fêmeas. **INTERAÇÕES:** **♦ Não foram conduzidos estudos de interação específicos com Xoterna Breezhaler.** A informação sobre o potencial de interações é baseada no potencial para cada uma das suas duas substâncias ativas. **♦ não deve ser administrado conjuntamente com bloqueadores beta-adrenérgicos** (incluindo colírios) exceto se existirem razões imperiosas para a sua utilização **♦ ovs fármacos conhecidos por prolongar o intervalo QT** podem aumentar o risco de arritmia ventricular **♦ a administração concomitante de outros agentes simpaticomiméticos** pode potenciar os efeitos indesejáveis **♦ o tratamento concomitante com derivados da metilxantina, corticosteroides ou diuréticos não-pouparadores de potássio** pode potenciar o possível efeito hipocalcémico dos agonistas beta-adrenérgicos **♦ a inibição dos principais contribuidores para a depuração do indacaterol, CYP3A4 e glicoproteína P (P-gp)** não tem impacto na segurança das doses terapêuticas **♦ a coadministração com outros medicamentos que contêm anticolinérgicos** não foi estudada e portanto não é recomendada **♦ não se esperam interações medicamentosas relevantes quando glicopirrônio é coadministrado com metidrina ou outros inibidores do transporte de catións orgânicos.** **EFEITOS INDESEJÁVEIS:** O perfil de segurança é caracterizado por sintomas beta-adrenérgicos e anticolinérgicos típicos relacionados com os componentes individuais da associação. Outras reações adversas mais frequentes relacionadas com o medicamento foram tosse, nasofaringite e cefaleias. **Reações adversas de Xoterna Breezhaler:** **♦♦ Muito frequentes (≥1/10):** infeção do trato respiratório superior. **♦ Frequentes (≥1/100, <1/10):** nasofaringite, infeção do trato urinário, sinusite, rinite, hipersensibilidade, hiperglicémia e diabetes mellitus, tonturas, cefaleias, tosse, dor orofaríngea incluindo irritação da garganta, dispnéia, cãibras dentárias, obstrução da bexiga e retenção urinária, pirexia¹², dor torácica. **♦ Pouco frequentes (≥1/1.000, <1/100):** angioedema, insónia, glaucoma¹³, doença cardíaca isquémica, fibrilhação atrial, taquicardia, palpitações, broncospasma paradoxal, disfonía, epistaxis, gastroenterite, xerostomia, prurido/exantema, dor musculoesquelética, espasmos musculares, mialgias, dor nas extremidades, edema periférico e fadiga. **♦ Raros (≥1/10.000, <1/1.000):** parestesias. ¹²Reação adversa observada com Xoterna Breezhaler mas não nos componentes individuais. **TITULAR DA AUTORIZAÇÃO DE INTRODUÇÃO NO MERCADO:** Novartis Europharm Limited. **REPRESENTANTE LOCAL:** Laboratório Medinfar-Produtos Farmacêuticos, S.A. 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Xoterna Breezhaler 2020-01-FL-08 elaborado em janeiro de 2020

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Deficiência de equilíbrio em indivíduos com DPOC: uma revisão sistemática com meta-análise

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2019-213608>)

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Received 21 May 2019
Revised 29 January 2020
Accepted 6 March 2020
Published Online First
14 May 2020



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Para citar: Loughran KJ, Atkinson G, Beauchamp MK, *et al.* Thorax 2020;75:539–546.

RESUMO

Contexto As pessoas com doença pulmonar obstrutiva crônica (DPOC) apresentam quatro vezes mais probabilidades de queda do que os seus pares saudáveis, o que conduz ao aumento da morbidade e mortalidade. Um equilíbrio fraco constitui um fator de risco importante para as quedas. Esta revisão visa quantificar a extensão da deficiência de equilíbrio na DPOC e estabelecer fatores clínicos contribuintes, que presentemente escasseiam.

Métodos Em julho de 2017, foram pesquisadas cinco bases de dados eletrônicas e, em março de 2019, foram efetuadas pesquisas atualizadas para estudos que comparassem o equilíbrio na DPOC com controlos saudáveis. Foram realizadas meta-análises sobre diferenças médias de amostra (DM), sendo também relatadas correlações entre o equilíbrio e fatores clínicos. A meta-regressão foi a ferramenta utilizada para quantificar a associação entre a diferença média em percentagem do volume expiratório forçado previsto em 1 segundo (FEV₁) e a deficiência de equilíbrio médio. Foram facultados resumos narrativos, onde os dados se revelaram insuficientes para meta-análise.

Resultados Foram incluídos vinte e três estudos (n=2751). A meta-análise indicou doentes com DPOC que apresentaram piores resultados comparativamente aos controlos saudáveis em termos de tempo no teste *up & go* (DM=2,77 seg, 95% IC 1,46 seg a 4,089 seg, p=<0,005), manter posição numa única perna (DM=-11,75 seg, 95% IC -15,12 seg a -8,38 seg, p=<0,005) e escala de equilíbrio de Berg (DM=-6,66, 95% IC -8,95 a -4,37, p=<0,005). O coeficiente de correlação combinado entre o equilíbrio e a força reduzida do quadríceps foi fraco-moderado (r=0,37, 95% IC 0,23 a 0,45, p=<0,005). A relação entre as diferenças percentuais estimadas de FEV₁ e equilíbrio foi negligenciável (r²=<0,04).

Conclusão Em comparação com os controlos saudáveis, as pessoas com DPOC apresentam uma redução do equilíbrio clinicamente significativa, que pode estar relacionada com a redução da força muscular, da atividade física e da capacidade de exercício. Os nossos resultados confirmam a necessidade de se aumentar o foco sobre a reabilitação pulmonar de modo a incluir a avaliação do equilíbrio e o treino e a explorar mais a deficiência de equilíbrio na DPOC.ional num desenho de estudo de não inferioridade.

Número de registo PROSPERO CRD4201769041.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is associated with breathlessness resulting in reduced exercise tolerance and poor health-related quality of life.¹ However, people with COPD are also four times more likely to fall than heal-

Mensagens-chave

What is the key question?

► What is the extent of balance impairment in COPD and what are the mechanisms underlying it?

What is the bottom line?

► Balance is impaired in people with COPD and this impairment is moderately associated with reduced strength and may be also be associated with reduced physical activity and exercise capacity.

Why read on?

► This is the first systematic review with metaanalyses to synthesise and quantify balance impairment and clinical associations in people with COPD highlighting important directions for future research.

thy peers, leading to increased morbidity, mortality and healthcare costs.^{2–5}

Balance impairment is a key risk factor for falls and people who fall have worse balance.⁶ However, individual studies have shown varying degrees of balance impairment in COPD.^{7–11} Reports also indicate more marked balance impairment following an acute exacerbation of COPD (AECOPD).^{10,12} However, studies investigating balance impairment in COPD are often underpowered and feature small samples sizes, and vary widely in outcomes used, and associated factors investigated, making it difficult to draw firm conclusions. It is unclear why balance is impaired in COPD; proposed contributing factors include reductions in proprioceptive control, trunk and respiratory muscle coordination, skeletal muscle dysfunction, reduced exercise capacity and physical activity levels, dyspnoea and systemic inflammation.^{8,10,12–17}

Despite increasing awareness of balance impairment, routine assessment is not part of international guidelines for COPD.¹ Nevertheless, the use of balance outcomes was briefly commented on by the American Thoracic Society/European Respiratory Society 'Key concepts in pulmonary rehabilitation' (PR)¹⁸ and treatment of balance impairment is becoming more frequent within PR with the emergence of effective balance training.¹⁹

The objectives of this systematic review are to; (1) Quantify the extent of balance impairment

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S1 (copd or chronic obstructive pulmonary disease) (54,471)
S2 (MH "Pulmonary Disease, Chronic Obstructive+") OR "copd" (59,309)
S3 (MH "Bronchitis Chronic") (1,619)
S4 emphysema (31,427)
S5 (MH "Emphysema+" OR (MH "Pulmonary Emphysema")) (25,822)
S6 "Balance" OR (MH "Postural Balance") (211,628)
S7 (MH "Gait+") OR (MH "Walking Speed") (22,099)
S8 walking (65,330)
S9 "gait impairment" (478)
S10 (MH "Postural Balance" OR (MH "Posture")) (73,685)
S11 postural control (5,276)
S12 S1 OR S2 OR S3 OR S4 OR S5 (84,921)
S13 S6 OR S10 OR S11 (266,426)
S14 S7 OR S8 OR S9 (78,098)
S15 S12 AND S13 (943)
S16 S12 AND S14 (1,617)
S17 S15 OR S16 (2,519)
S18 17 OR 18 Limiters - English Language (2,246)

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Figure 1 Example search strategy performed in MEDLINE.

in COPD compared with healthy controls, when data are synthesised across studies, and (2) Explore which clinical factors contribute to balance impairment in COPD. Results will inform development of targeted assessment and treatment strategies to improve balance and reduce fall risk in COPD.^{3 4 20}

MATERIALS AND METHODS

The review was registered on PROSPERO in June 2017 and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.²¹

Search strategy

Figure 1 shows the search strategy. Searches of MEDLINE, CINAHL, AMED, Scopus and EThOS were undertaken by KL, after health librarian consultation, in July 2017 and updated in March 2019. The review initially included both balance and gait as falls occur during static and dynamic activities. However, due to the large volume of articles found, this review focus is balance only. The results of studies reporting gait outcomes were excluded and will be presented in a separate systematic review on gait impairment. This systematic review will provide an update, and meta-analysis in addition to that presented in a previous systematic review on gait analysis in COPD.²²

Selection of articles, data extraction, risk of bias and quality assessment

Inclusion criteria was informed by PICO; population – adults with a primary diagnosis of COPD by GOLD criteria,¹ comparison – healthy controls, outcomes – static (eg, posturography) or dynamic balance measures (eg, berg balance scale (BBS), single leg stance (SLS) and timed up and go (TUG)), that is, functional balance measures in a single activity or a standardised scoring system. Grey literature, case study reports, commentary, conference abstracts, reviews and study protocols were included and reference lists were handsearched. Measures where balance is one aspect of a global functioning instrument, and non-English language articles were excluded. Falls outcomes were also excluded as they detect the risk or quantity of falls and do not indicate the extent or nature of balance problems that may result in a fall. All screening and full text reviews were undertaken by two pairs (KL, SLH and MKB, SR). Data were extracted by KL and verified by SLH using a standardised template. Any discrepancies were resolved by consensus. A quality assessment including questions on risk of bias, was undertaken (by KL, SLH) using the Downs and Black tool.²³ As studies were not testing interventions no intervention questions were included, thus the maximum score was 18. An analysis of small study effects (publication bias) was performed on studies included in the meta-analyses.

Data analysis

Outcomes reported in five or more studies²⁴ were included in meta-analyses and meta-regressions using Comprehensive MetaAnalysis Software (CMA V3). Reported conversion equations^{25 26} were used to calculate means (SD) from medians (IRQ)

in three studies, assuming that departures from Gaussian distributions were not severe. When data were reported solely for subgroups, pooled study effect sizes and SDs were estimated using reported equations.²⁷ Authors were contacted when data were unusually different from other studies data and when there were extreme outliers or concerns of data reporting errors. One author reported that data were not available, and no response was received from other contacted authors, thus sensitivity analyses were undertaken with and without these studies data. Mean differences (MD) were compared with previously published minimal clinically important difference (MCID) values for COPD.^{28–30}

Random effects meta-analyses were undertaken using differences in sample means as outcomes. Second, a meta-regression was performed on all studies that were in the meta-analyses to quantify the extent that study mean disease severity (using the mean difference in percentage predicted forced expiratory volume in 1 s (FEV₁) between COPD and healthy controls in each study) was associated with study mean balance impairment. Finally, a meta-analysis of reported Pearson's correlation coefficients reported in each study for the association between balance impairment and strength in each study sample was performed. Low study numbers prevented the analysis of other factors. Ninety-five per cent CIs and prediction intervals were reported,³¹ and heterogeneity was quantified using the I² and Tau statistics.^{32 33} Posturography studies, featuring heterogeneity in measurement units and test conditions, rendered meta-analysis inappropriate. The remainder of clinical balance outcomes are reported as narrative summaries along with AECOPD results. The presence of small study effects were explored for using a Funnel plot and Egger's regression analysis.

RESULTS

Electronic literature search results

Of 11506 search results, 3904 titles were screened, 75 full texts were assessed for eligibility (including one identified by hand-searching reference lists and two identified during the updated searches) and 23 studies were included (see figure 2).

Description of studies, risk of bias and quality assessment

Study characteristics are reported in online supplementary table 1. Seventeen studies featured clinical balance outcome measures; BBS, (n=8), BESTest (n=1), Mini BESTest (n=1), Tinetti (n=2), TUG, (n=9), SLS (n=6), Functional Reach Test (n=2) and Community Balance and Mobility Scale (CBMS) (n=1), six of these studies used more than one clinical balance outcome. Posturography featured in 13 studies, 7 of those combining posturography with clinical balance outcome measure.

Quality scores ranged from 10 to 14 (see online supplementary table 2). Frequent issues included low external validity and confounding internal validity, due to poor reporting of sample selection and characteristics, and lack of a power calculation. Due to the narrow range of quality scores adjustment for study quality was not made. Seven studies featured adjustments for confounders (see table 1 for details). The results for small study effects (an indicator of publication bias) were; TUG=Egger's regression intercept 2.65 (95% CI –7.35 to 12.66), p=0.28; SLS=Egger's regression intercept –1.11, (95% CI –4.26 to 2.02), p=0.19; BBS=Eggers regression intercept –3.50, (95% CI –9.62 to 2.62), p=0.10 (see figure 3).

Balance impairment in stable COPD

A meta-analysis comparing balance in COPD versus healthy controls was performed for the TUG (n=9), SLS (n=6) and BBS (n=8) (including stable and control groups from studies investigating AECOPD, stable COPD and healthy controls). People

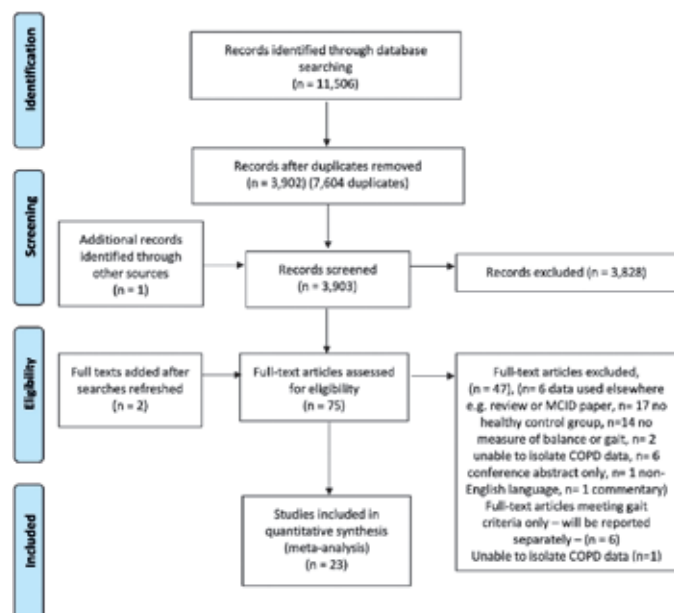


Figure 2 Preferred Reporting Items for Systematic Reviews and MetaAnalyses diagram.

with COPD had poorer performance on the TUG, (MD=2.77s, 95%CI 1.46s to 4.089 s, Tau=1.93, Q value =181.87, I² = 95.60, p<0.005, n=582) (figure 4), SLS, (MD=-11.75s, 95%CI -15.12s to -8.38 s, Tau=3.22, Q value=17.00, I² = 70.59, p<0.005, n=288) (figure 5) and BBS, (MD=-6.66, 95%CI -8.95 to -4.37, Tau 3.03, Q value= 64.62, I²=89.17, p<0.005, n=512) (figure 6). MCIDs in COPD for the TUG, SLS and BBS are 2.68s, -4.03s and -3.5, respectively,^{28–30} and all were exceeded. Table 1 summarises the sensitivity analyses which had little effect on outcomes. The 95% prediction intervals for the TUG, SLS and BBS MDs were -1.92 to 7.46, -21.13 to -2.37 and -14.31 to 0.98, respectively.

Balance deficits were reported to be greater in COPD in seven out of eight studies using clinical balance measures not included in the meta-analyses. The seven studies (n=1899) used; BESTest (MD 21.3, 95%CI 17.1 to 25.4, p<0.001),¹¹ Mini BESTest (p<0.005) and TUG with dual task (p=0.0005),³⁴ CBMS Scale (p=0.001),³⁵ Tinetti test (p<0.001 and p<0.05)^{36,37}

and Functional Reach Test (p≤0.001, and 3.0cm, p<0.0001, 95%CI -4.2 to -1.8).^{14,38} One study using the standing balance test (n=35 participants) reported no difference (p value unavailable).⁹

People with COPD performed worse on posturography in 8 out of 11 studies. Three studies reported slower postural responses in COPD; responses to perturbations were slower (MD 49ms, 95%CI 6 to 91, p=0.027),¹¹ return to baseline of COPD after arm movements were slower (p=0.023)¹⁷ and standing phase of sit-to-stand-to-sit (STSTS) (p=0.028) and stand-to-sit phase of STSTS was slower (p=0.001).¹³ One study demonstrated a reliance on ankle over back proprioceptive strategy (p=0.047).⁸ Four studies reported worse postural control in COPD; SLS on a balance platform (p=0.01),³⁹ quiet standing with and without vision (p=0.005 and p=0.005),³⁴ static balance standing on foam (p<0.05)¹⁵ and static balance over various conditions before (p<0.042) and after (p=0.040) upper limb exercise⁴⁰ (n=432 across all eight studies). Three studies reported no difference between COPD and control groups (p values unavailable)^{37,41,42} (n=223).

The Sensory Organisation Test (SOT) for balance using posturography showed greater overall balance impairment in COPD in one study (p=0.016)⁴³ and on only one test condition (eyes open moving platform) in another (p<0.05 and unavailable)³⁵ (n=91). However, no one sensory system was able to explain variability in balance control.^{35,43}

Balance impairment in AECOPD

Three studies compared BBS, TUG, SLS and posturography in three groups; people with COPD who were experiencing an AECOPD, people with stable COPD and in healthy controls. All three studies reported worse balance impairment during AECOPD compared with healthy controls (n=175) when using both dynamic (p<0.001)^{10,12} and static balance measures (p≤0.05).¹⁵ Balance was reported to be further impaired during AECOPD when compared with stable COPD, in two of the three studies, using dynamic balance measures (p<0.001 in both^{10,12}) (n=124). The third study reported no difference in balance impairment between stable COPD and AECOPD measured with BBS (p value unavailable). Postural sway, measured by

Table 1 Summary of sensitivity analysis results

Outcome	Study removed	Reason for removal	Difference in means	SE	CI lower limit	CI upper limit	P value	Heterogeneity
TUG	None	N/A	2.773	0.671	1.457	4.089	<0.005	I ² =95.601, Tau=1.929, Q value=181.868, p<0.005
TUG	Butcher <i>et al</i> 2004 ³⁵	SE converted to SD	2.985	0.743	1.529	4.441	<0.005	I ² =95.972, Tau=2.001, Q value=173.763, p<0.005
TUG	Crišan <i>et al</i> 2015, Voica <i>et al</i> 2016 ⁶³ and Tudorache <i>et al</i> 2015 ^{10,12}	IQR and medians converted to mean and SD	1.742	0.517	0.729	2.755	0.001	I ² =90.748, Tau=1.185, Q value=54.045, p<0.005
SLS	None	N/A	-11.754	1.720	-15.124	-8.384	<0.005	I ² =70.583, Tau=3.222, Q value=16.997, p=0.005
SLS	Butcher <i>et al</i> 2004 ³⁵	SE converted to SD	-12.809	1.793	-16.324	-9.295	<0.005	I ² =71.539, Tau=3.117, Q value=14.054, p=0.007
SLS	Crišan <i>et al</i> 2015, Voica <i>et al</i> 2016 and Tudorache <i>et al</i> 2015 ^{10,12}	IQR and medians converted	-9.236	2.747	-14.620	-3.853	0.001	I ² =42.297, Tau=3.157, Q value=3.466, p=0.177
BBS	None	N/A	-6.659	1.168	-8.947	-4.371	<0.005	I ² =89.168, Tau=3.028, Q value=64.622, p<0.005
BBS	Crišan <i>et al</i> 2015, Voica <i>et al</i> 2016 and Tudorache <i>et al</i> 2015 ^{10,12}	IQR and medians converted	-7.110	1.617	-10.279	-3.941	<0.005	I ² =92.110, Tau=3.397, Q value=50.697, p<0.005
BBS	Porto <i>et al</i> 2017 ⁴²	SE converted to SD	-7.110	1.332	-9.720	-4.499	<0.005	I ² =90.453, Tau=3.254, Q value=62.847, p<0.005
BBS	Ozalevli <i>et al</i> 2011 ¹⁶	Outlier	-5.101	0.703	-6.479	-3.724	<0.005	I ² =68.575, Tau=1.477, Q value=19.093, p=0.004

BBS, berg balance scale; SLS, single leg stance; TUG, timed up and go.

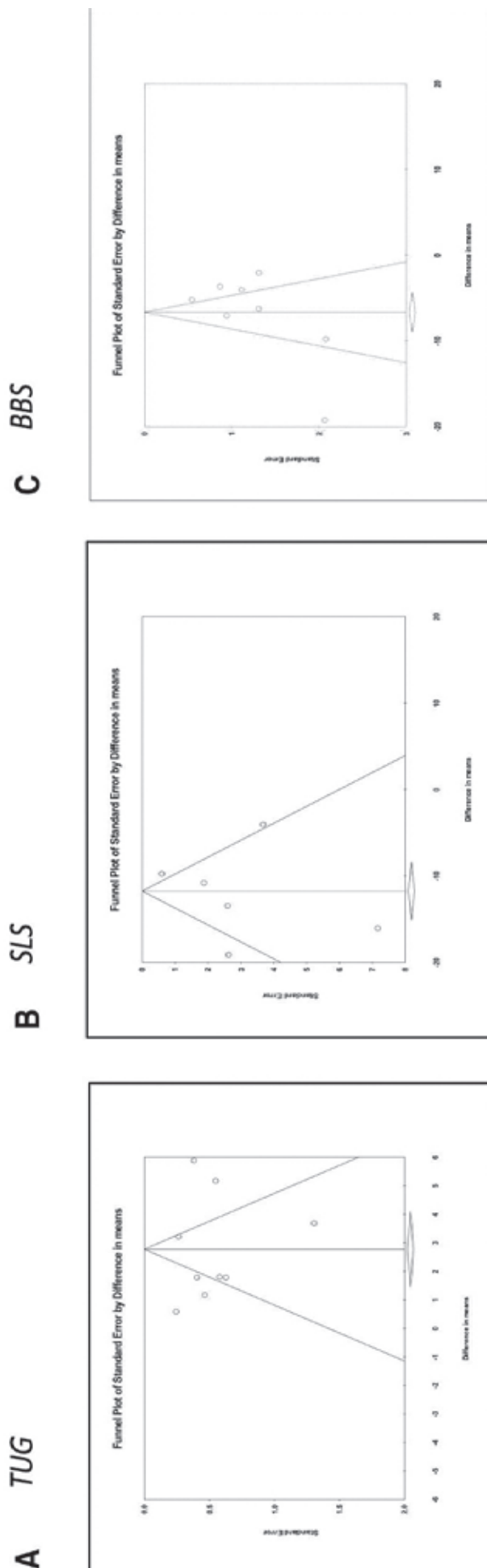


Figure 3 Funnel plot of assessments of small study effects (publication bias) for (A) TUG, (B) SLS, and (C) BBS. BBS, berg balance scale; SLS, single leg stance; TUG, timed up and go.

posturography in this study,¹⁵ was impaired in all four standing conditions examined (normal standing, eyes closed, feet together and foam base) in AECOPD and only in foam base standing in stable COPD, additionally 30% (n=8) of the AECOPD group and 7% (n=2) of the stable COPD group were unable to perform the foam standing condition or refused to attempt it due to poor balance confidence (p value unavailable between AECOPD and stable COPD results were not reported, n=51).¹⁵

Factors associated with balance impairment

Meta-analysis was performed on reported correlations of balance measures (TUG, BBS, SLS, and BESTest) with quadriceps strength (peak torque Nm/kg, kg of force, Newton metres, and 0 to 5 manual scale testing). A weak-to-moderate pooled association was detected between increased balance impairment and reduced quadriceps strength ($r=0.37$, 95%CI 0.23 to 0.50, $\text{Tau}=0.00$, Q value 3.98, $I^2=0.00$, $p<0.005$, $n=271$) (figure 7). One study investigating balance during AECOPD found reduced BBS scores ($r=0.51$, $p=0.01$)¹⁵ and worse sway on an unstable surface were associated with reduced quadriceps strength ($r=0.53$ and 0.53 , $p<0.05$, $n=51$).¹⁵

Two out of three studies investigating balance impairment and reduced physical activity (PA) levels reported an independent association with SLS and daily steps ($r=0.821$, $p=0.001$) and moderate-to-vigorous PA ($r=0.645$, $p=0.014$).⁹ Physical Activity Scale for Elderly (PASE) scores were positively associated with BBS scores ($r=0.41$, $p=0.007$) and BESTest scores ($r=0.40$, $p=0.008$)¹¹ ($n=86$). A third study reported no association with postural control deficits on SOTs in COPD ($n=40$) and PA, but there was no significant difference in PASE scores ($p>0.05$) between COPD and control groups (r and p values unavailable).⁴³ Three studies investigated balance impairment and exercise capacity and all reported that shorter 6MWDs were correlated with poorer performance on clinical balance outcomes; BBS ($r=0.61$, $p<0.01$),¹⁶ TUG ($r=0.43$, $p=0.002$)³⁹ and SLS ($r=0.504$, $p=0.017$)⁹ ($n=163$). Two studies reported worse balance outcomes with fatigue; after upper limb exercise,⁴⁰ and with leg fatigue severity ($r=0.38$, $p<0.05$)¹⁶ ($n=88$ participants).

A meta-regression identified no clear association between mean disease severity and clinical balance outcomes (TUG intercept -1.23 , $p=0.70$, 95% CI -7.68 to 5.22 , $I^2=95.20\%$, $n=582$, SLS intercept -14.99 , $p=0.17$, 95%CI -36.29 to 6.30 , $I^2=74.53\%$, $n=288$, BBS intercept -4.68 , $p=0.48$, 95% CI -17.76 to 8.39 , $I^2=90.46\%$, $n=512$). FEV_1 and other measures of disease severity were associated with balance impairments in five studies ($n=429$) which used; FEV_1 with posturography ($p<0.005$, $r=0.416$ and 0.479) and CBMS ($p=0.586$);³⁵ CAT score and BBS ($p=0.03$, $\gamma=0.24x+42.3$);¹⁰ severity of COPD with slower postural responses in an anteroposterior direction ($p=0.031$);¹⁷ BODE Index with Tinetti ($p<0.05$, $r=-0.78$);³⁷ lower oxygen saturation after 6MWD ($r=0.30$, $p<0.05$) and partial arterial oxygen pressure before exercise with BBS ($r=0.28$)¹⁶ ($n=238$). However, four studies reported no associations between balance and disease severity (FEV_1) or hypoxia; with Mini BESTest ($p>0.41$);³⁴ GOLD stages or BODE index³⁹ with people unable to complete a SLS with or without supplementary oxygen (p value unavailable);³⁵ number of anteroposterior and mediolateral postural adjustments, and postural responses by disease severity ($p>0.28$)¹⁷ ($n=221$).

Results of further clinical associations are limited by small study numbers and are presented in an e-supplement (online supplementary file 3), these are; inspiratory muscle strength, dyspnoea, anxiety, depression, inflammation, COPD phenotype, body mass index, vitamin D, sex and gait quality.

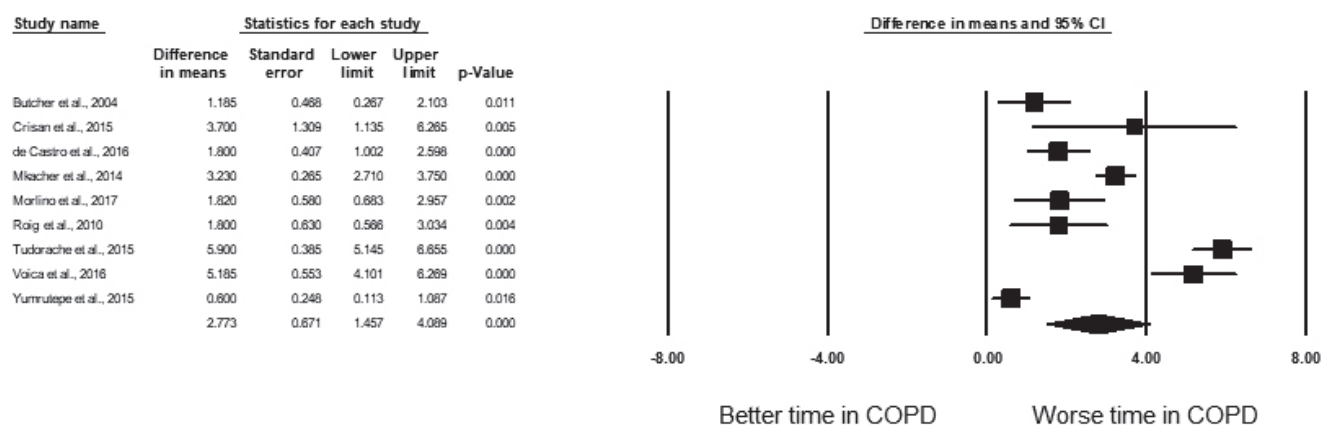


Figure 4 Meta-analysis of timed up and go scores in people with COPD versus healthy controls.

DISCUSSION

Pooled analyses of the most frequently used clinical balance measures (TUG, SLS and BBS) showed both statistical and clinically important balance deficits in COPD compared with healthy controls.^{44,45} Posturography measures were common but measurement and design varied widely limiting between-study comparisons. Fewer studies have examined balance impairment during AECOPD and no firm conclusions can be made. Balance impairment was associated with reduced strength, but not disease severity.

This review reports a high magnitude of balance impairment in people with COPD using robust and commonly used balance outcomes. There are however, known ceiling effects of the BBS and SLS^{44,45} potentially underestimating the extent of balance impairment. Balance impairment is one of the strongest independent risk factors for falls which are a predictor of mortality in COPD,⁴⁶ however balance exercises are not routinely provided as part of PR. Balance training incorporated into PR is feasible and effective,^{19,47–49} not only for improving balance but also general physical function, although there remain few studies in this area. Our findings support a need for expanding the focus of rehabilitation to include balance and further exploration of balance and falls in COPD.

Although less conclusive, posturography studies also indicated balance impairment in COPD. Posturography is less functional than clinical balance measures and does not typically identify dynamic balance impairment, potentially explaining inconclusive results. However, posturography studies using SOTs were able to rule out sensory issues as a mechanism for balance impairment. Additionally, posturography studies looking at specific mechanisms like reaction

times and joint motions at ankles and hips/ back were more likely to highlight problems with neuromuscular control of balance.^{11,17} This finding is consistent with literature indicating that ankle over back strategy, which becomes less efficient in older age as nerve conduction slows,⁵⁰ may be relied on by people with COPD due to musculoskeletal changes around the trunk.^{17,51,52}

Reduced strength is a common systemic effect of COPD⁵³ which may partly explain why balance is impaired. The majority of studies have investigated quadriceps strength despite other muscle groups having a role in balance, for example, trunk, hip and ankle muscles.^{8,17} There may be an association between balance and reduced PA and exercise capacity which could impair balance by contributing to disuse of balance systems, including postural control muscles. Conversely, balance impairments may impact on PA and exercise capacity by reducing functional ability or increasing fear of falling.⁵⁴ Considering the negative findings of disease severity, we suggest balance impairment is multifactorial, relating to secondary impairments of disease interplaying with the effects of normal ageing on balance such as neuropsychological changes,⁵⁵ and increasing chronic pain.^{56,57} Mechanisms underlying the deficits observed in COPD require further investigation including research into other contributing factors given the underwhelming strength of these associations.

Evidence for further balance impairment during AECOPD is scarce but supported by two of the three AECOPD studies included. An AECOPD may impair balance further as strength and PA are reduced post-AECOPD.⁵⁸ More studies are needed to fully elucidate the impact of AECOPD on balance including the feasibility, safety and role of early assessment and inter-

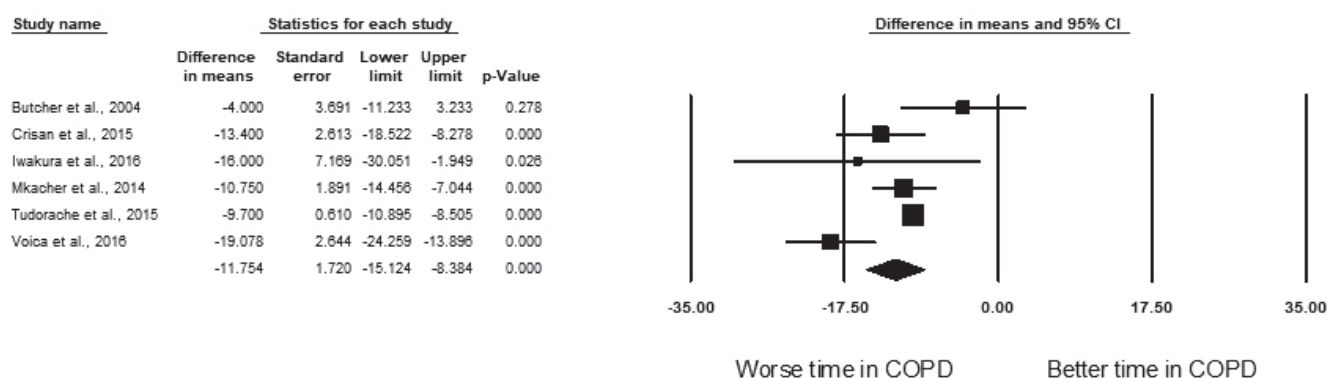


Figure 5 Meta-analysis of single leg stance times in people with COPD versus healthy controls.

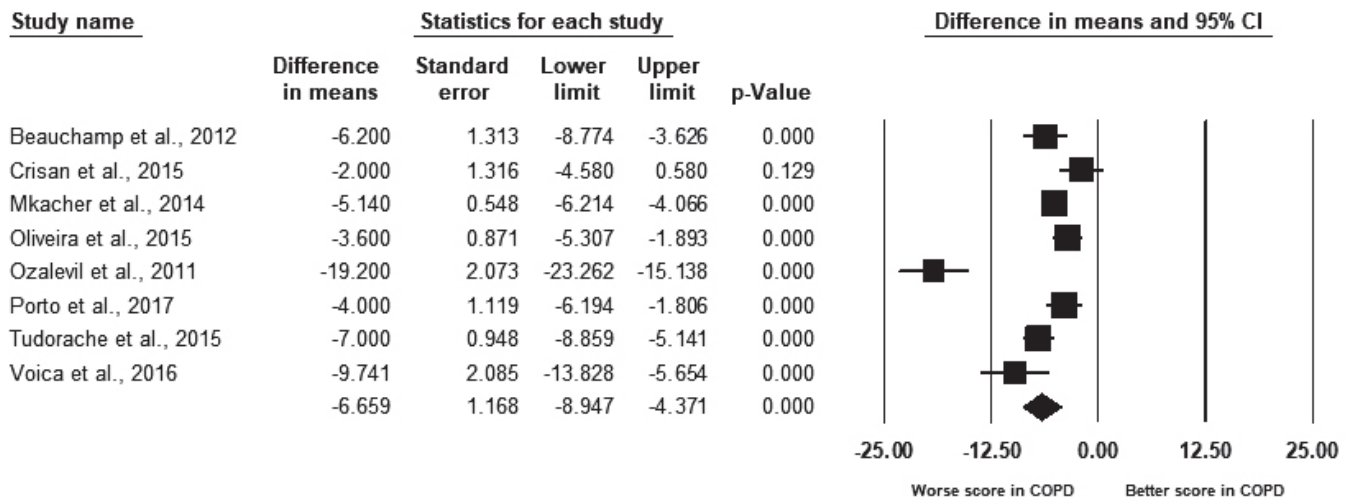


Figure 6 Meta-analysis of berg balance scale scores in people with COPD versus healthy controls.

vention of balance to ensure patients are not hindered by poor balance and falls when aiming to return to their pre-exacerbation strength and PA levels.

This review featured a wide-reaching search strategy and four reviewers; thus, missed studies are unlikely, and a strong inclusion consensus was reached. While meta-analysis revealed a large effect there was heterogeneity between studies as demonstrated by Tau and Prediction Intervals thus results should be interpreted with this in mind. COPD is a disease that features different phenotypes, subgroups and clusters of clinical characteristics, that vary in physiological, psychological and socioeconomical factors.^{59–61} None of the studies included any measurement of, or adjustment for phenotypic differences. It is plausible that balance impairment affects different phenotypes to differing degrees. Additionally, other population variances were poorly reported and the majority of studies did not adjust for common confounders; with quality issues common again caution is advised regarding the results. However, a number of sensitivity analyses were performed which did not vary effect sizes or heterogeneity significantly. Meta-analysis of means, including regression analysis, was performed at study level which is a less robust approach.

However, meta-analysis on correlations included individual level data, considered a 'deft' approach⁶² and the use of five studies minimum for meta-analysis enhanced the robustness. A limited number of studies reporting data on sex and a narrow age range across studies prevented adjustments for both and the MCIDs used were developed based on within-subject change as none are available for between subject differences. The meta regressions were performed on a relatively low number of studies (n=9, n=6 and n=8 respectively) which were below the 10-study minimum recommended by the Cochrane Handbook for Systematic Reviews, therefore further investigation of the effect of disease severity is required, especially because we could not detect any clear meta-regression associations so these particular analyses may have been influenced by low statistical power. Meta-analysis was impossible for posturography. Strength measurements included less accurate measurements such as manual muscle strength testing, which was one of the weakest correlations perhaps underestimating the strength and balance association.

Researchers should improve quality by performing power calculations and reporting details of populations, participant selection and confounder adjustments. Agreement on out-

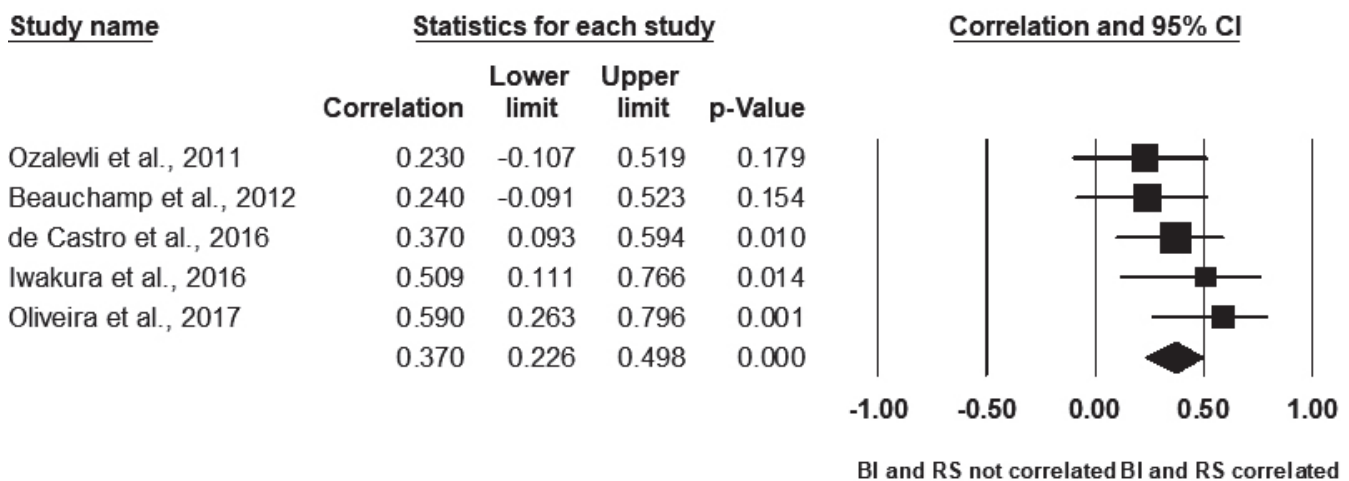


Figure 7 Meta-analysis of reduced quadriceps strength and balance impairment correlations in people with COPD. BI= Balance Impairment; RI = Reduced Strength.

comes is needed across studies to improve comparability. Studies should investigate links between balance and strength, PA, exercise capacity and other possible modifiable mechanistic factors, and, given that they are reduced after AECOPD, work is required to see if balance is worse after hospital discharge.

CONCLUSIONS

People with COPD have extensive balance impairment which may be associated with reduced muscle strength, PA and exercise capacity. Balance may be worse during AECOPD, but evidence is scarce. More work is required to understand the mechanisms underlying balance deficits in COPD, including the investigation of novel clinical factors. Balance assessment and available interventions^{19 47} should be incorporated into international guidelines for COPD care.¹

Acknowledgements The authors would like to thank Dr scotty Butcher (school of rehabilitation science University of saskatchewan, canada) and Dr Cristiano Carneiro Oliveira (Departamento de Fisioterapia, Universidade Federal de Juiz de Fora, Brazil) for providing additional information regarding their studies and Dr ryan Kenny (Teesside University, Middlesbrough, UK) for advice on analysis of posturography data.

Contributors Kl, slh, MKB, JD and DM contributed to study conception and protocol of the review. Kl, slh, MKB and sr performed the systematic review. Kl and ga performed the statistical analysis. Kl, slh, ga, MKB, JD and DM contributed to the interpretation of data. Kl drafted the paper and all authors provided critical revisions and contributed to the editing of the paper.

Funding The lead author is undertaking doctoral studies funded in association with the Universities alliance Doctoral Training alliance for Biosciences. M Beauchamp is supported by an emerging research leaders award from the canadian respiratory research network.

Competing interests none declared.

Patient consent for publication not required.

Provenance and peer review not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request to the corresponding author.

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A espirometria realizada como parte do programa comunitário de rastreio do cancro do pulmão em Manchester deteta uma elevada prevalência de obstrução do fluxo aéreo em indivíduos sem diagnóstico anterior de DPOC

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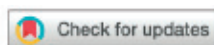
Received 18 May 2019

Revised 29 April 2020

Accepted 30 April 2020

Published Online First

22 May 2020



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Para citar: Balata H, Harvey J, Barber PV, et al. Thorax 2020;75:655–660.

RESUMO

Contexto A DPOC é uma das principais causas de morbilidade e mortalidade nas populações elegíveis para o rastreio de cancro do pulmão. Investigámos o papel da espirometria num programa comunitário de rastreio de cancro do pulmão.

Métodos Fumadores, de 55–74 anos, residentes em três áreas desfavorecidas de Manchester foram convidados para um “exame de saúde pulmonar” que se realizou em locais convenientes para a comunidade. A espirometria foi incorporada no exame, juntamente com a estimativa do risco de cancro do pulmão (*Prostate, lung, colorectal e Ovarian study risk Prediction Model*, 2012 version (PLCO_{M2012})), a avaliação dos sintomas e os conselhos para a cessação do tabagismo. Os participantes com elevado risco de cancro do pulmão (PLCO_{M2012} ≥ 1.51%) foram elegíveis para o rastreio anual de CT de dose reduzida em duas rondas de rastreio. A obstrução do fluxo aéreo foi definida como FEV₁/FVC < 0.7. As bases de dados de cuidados primários foram pesquisadas para qualquer diagnóstico prévio de DPOC.

Resultados 99,4% (n=2525) dos participantes do exame pulmonar realizaram espirometria com sucesso. A idade média foi de 64,1±5,5, 51% eram mulheres, 35% eram fumadores habituais. 37,4% (n=944) apresentaram obstrução do fluxo aéreo, dos quais 49,7% (n=469) não apresentaram diagnóstico prévio de DPOC. 53,3% das pessoas sem diagnóstico prévio eram sintomáticas (n=250/469). Após análise multivariada, a deteção de obstrução do fluxo aéreo sem diagnóstico prévio de DPOC foi associada ao sexo masculino ($_{adj}OR$ 1,84, 95% IC 1.37 a 2,47; $p < 0,0001$), idade mais jovem ($p = 0,015$), menor duração do tabagismo ($p < 0,0001$), menor número de cigarros por dia ($p = 0,035$), maior relação FEV₁/FVC ($< 0,0001$) e ser assintomático ($_{adj}OR$ 4,19, 95% CI 2,95 a 5,95; $p < 0,0001$). A probabilidade de cancro do pulmão detetado no rastreio foi significativamente superior nas pessoas com evidências de obstrução do fluxo aéreo com diagnóstico prévio de DPOC ($_{adj}OR$ 2,80, 95% IC 1,60 a 4,82; $p = 0,002$).

Conclusões A incorporação da espirometria num programa comunitário de rastreio de cancro do pulmão é viável e identifica um número significativo de indivíduos com obstrução do fluxo aéreo sem diagnóstico prévio de DPOC.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a significant global health problem

Mensagens-chave

What is the key question?

- Is it feasible to incorporate spirometry into a community-based lung cancer screening programme in order to detect previously undiagnosed airflow obstruction?

What is the bottom line?

- Incorporating spirometry into a community-based cancer screening programme, targeting high-risk populations, is feasible and identifies a significant number of individuals with airflow obstruction without a prior diagnosis of COPD.

Why read on?

- Our study demonstrates how a ‘Lung Health Check’ approach to lung cancer screening, which includes spirometric assessment for undiagnosed COPD, can successfully reach individuals of low socioeconomic status from deprived areas and therefore provide an opportunity to address other smoking-related causes of morbidity and mortality in high-risk populations.

and a leading cause of morbidity and mortality with a considerable economic burden.^{1,2} The World Health Organization (WHO) has projected that deaths attributable to COPD will increase by up to 30% over the next 10 years and become the third leading cause of death across the globe.³ Tackling the prevalence of smoking, which is the most important risk factor for developing COPD, is a key goal.^{3,4} Individuals diagnosed with COPD often suffer from breathlessness, chronic cough and sputum production; however, during the early stages of the disease, it is often asymptomatic. COPD is therefore commonly underdiagnosed and also often misdiagnosed in primary care settings with reported prevalence rates ranging from 3.6% to 19%.^{5,6}

Individuals with undiagnosed COPD are at increased risk of exacerbations and pneumonia; those with symptoms are also at increased risk of death.⁷ Understanding factors associated with delayed or missed diagnosis is therefore impor-

tant.⁸ The burden on the healthcare system for the management of exacerbations is equivalent for individuals with airflow obstruction irrespective of previous COPD diagnosis.⁹ Diagnosis of COPD at an earlier stage may improve outcomes and quality of life⁴ although screening for asymptomatic COPD is not currently recommended.¹⁰ Characteristics reported to be associated with missed COPD diagnosis include: younger age, male gender, lower symptom burden, current smoking, lower education and having better lung function.^{6,7} For individuals with the relevant exposures and symptoms, spirometry is required to make the diagnosis. The key spirometric finding is airflow obstruction; this is defined as a postbronchodilator ratio of FEV_1 to FVC of <0.7 .⁴

Lung cancer is the world's leading cause of cancer death and most patients are diagnosed at an advanced incurable stage primarily due to late presentation.¹¹ Low-dose CT (LDCT) screening of high-risk smokers reduces lung cancer-specific mortality and a recently published position statement from European investigators recommended implementation of screening across Europe.¹² The link between COPD and lung cancer is well established¹³ and the prevalence of COPD within lung cancer screening programmes well described.^{14–17} However, spirometry is not routinely incorporated into screening programmes. Including assessments for other smoking-related comorbidities such as COPD in screening programmes has the potential to improve cost effectiveness.¹⁸ Successful implementation of lung cancer screening will require services to be accessible to those at greatest risk, such as smokers with low socioeconomic status (SES).¹⁹ Low SES is associated with higher levels of smoking, COPD and lung cancer but also reduced participation in screening trials.^{20,21} We developed a 'Lung Health Check' programme which took place in deprived community locations across Manchester to try to address this participation bias and overcome practical barriers such as cost, distance and travel.²² The aim of this study was to determine whether incorporating spirometry into a community-based lung cancer screening programme was effective in identifying individuals with previously undetected airflow obstruction, and therefore possible COPD. We also wanted to explore the characteristics of individuals with airflow obstruction to see if there are important differences between those that do and those that do not have a prior diagnosis of COPD. We hypothesise that incorporating spirometry into a lung cancer screening programme would be feasible and would identify a significant number of attendees with previously undetected airflow obstruction.

METHODS

Manchester Lung health Checks

A detailed description of the Manchester Lung Health Check pilot has previously been published.^{23,24} In brief, ever smokers aged 55–74 registered with participating general practitioner (GP) practices were invited to attend an LHC in convenient community locations, across three sites, in deprived areas of Manchester. As part of the LHC, participants underwent an assessment of respiratory symptoms, spirometry and a calculation of their 6-year lung cancer risk score using the Prostate, Lung, Colorectal and Ovarian Study Risk Prediction Model, 2012 version (PLCO_{m2012}).²⁵ This model takes several parameters into account including age, gender, ethnicity, smoking exposure, education, body mass index, previous medical and family history. Those at a higher risk of lung cancer, defined as a PLCO_{m2012} score of $\geq 1.51\%$,²⁶ were invited to participate in annual LDCT screening over two screening rounds. Postcodes were recorded to determine Index of Multiple Deprivation 2015 (IMD) rank for England. This is a measure of relative deprivation in small areas (neighbourhoods) of England; areas are ranked from 1 (most deprived) to 32844 (least deprived).²⁷ Healthcare records were searched for a diagnosis of lung cancer

using International Classification of Diseases (ICD) codes in all those lost to follow-up in the second round of screening.

Spirometry

Spirometry was performed in accordance with Association for Respiratory Technology & Physiology (ARTP) guidelines²⁸ at the time of the LHC using a desktop spirometer (Vitalograph ALPHA). All nurses performing spirometry had undergone formal ARTP training. All measures were prebronchodilator and included FEV_1 , FVC and their respective Global Lung Function Initiative reference values. Each participant was given at least three attempts at performing spirometry and the highest value recorded. Airflow obstruction was defined as an FEV_1 /FVC ratio <0.7 .⁴

Symptom questionnaire

Participants were asked about respiratory symptoms at the time of the LHC including: breathlessness (using the Medical Research Council (MRC) dyspnoea scale), cough (including duration), sputum production, wheeze, haemoptysis, chest pain and antibiotic or steroid use for exacerbations (≥ 2 episodes per year). In accordance with Global Initiative for Chronic Obstructive Lung Disease recommendations, participants were categorised as 'symptomatic' if they reported any one or more of the following symptoms: breathlessness (MRC dyspnoea scale ≥ 2), chronic cough (≥ 6 weeks) or regular sputum production ($\geq$ teaspoon/day).⁴

Definition of COPD

For the purpose of these analysis, individuals were categorised as potentially having COPD if they had airflow obstruction, independent of presence and pattern of symptoms. Participants were asked if they had ever been diagnosed with COPD or emphysema and primary care records were searched for a prior diagnosis of COPD, emphysema or chronic bronchitis using ICD codes in all those with airflow obstruction; those without a prior diagnosis were categorised as 'undiagnosed'.

LDCT and radiological reporting

All LDCT scans (Optima 660, GE Healthcare) were reported by National Health Service Consultant Radiologists with a specific interest in thoracic radiology. As part of the reporting template, other respiratory radiological findings were recorded including the presence or absence of emphysema. Such findings were reported at the discretion of the reporting radiologist without predefined definitions. The severity or form of emphysema was not recorded.

Statistical analysis

All statistical analysis was conducted using SPSS V.22. Groups were compared using independent t-test (parametric) or MannWhitney U test (non-parametric) for continuous data and χ^2 and Fisher's exact tests for categorical data. We tested whether the presence of airflow obstruction was independently predictive of lung cancer after 2 years of follow-up by undertaking a logistic regression analysis including PLCO_{m2012} score (as this model includes a number of variables associated with lung cancer risk).

In further analyses limited to those with airflow obstruction, we performed univariate binary logistic regression to determine whether standard clinical variables differed between individuals with airflow obstruction who did or did not have a prior COPD diagnosis. Variables with a significant association ($p \leq 0.05$) were then entered into a multivariate model. We also tested whether a GP diagnosis of COPD was independently predictive of lung cancer by undertaking a logistic regression analysis including PLCO_{m2012} score. Statistical significance was defined as $p \leq 0.05$.

Table 1 Baseline characteristics of all participants stratified according to previous COPD diagnosis in those with obstructive spirometry

Variable	No airflow obstruction	Airflow obstruction	P value	Airflow obstruction (n=944)		P value
				Undiagnosed COPD	Diagnosed COPD	
Number of participants (%)	1581 (62.6)	944 (37.4)	–	469 (49.7)	475 (50.3)	–
Smoking status						
Current (%)	422 (27)	462 (49)	<0.001	213 (45)	249 (52)	0.031
Former (%)	1159 (73)	482 (51)	<0.001	256 (56)	226 (48)	
Smoke duration (years)	31±15	40±13	0.39	37±13	43±12	<0.001
Sex male (%)	796 (50)	492 (52)	<0.001	242 (52)	210 (44)	0.023
Mean age (years) ±SD	63.6±5.5	65.0±5.4	0.004	64.5 (5.4)	65.5 (5.4)	0.003
Median IMD rank	2908	2806	<0.001	2848	2693	0.399
Self-report COPD	193 (12)	368 (39)	<0.001	0	368 (78)	<0.001
Symptomatic (%)	865 (55)	639 (68)	<0.001	250 (53)	389 (82)	<0.001
Cough (%)	466 (30)	393 (42)	<0.001	144 (31)	249 (52)	<0.001
Sputum (%)	493 (31)	455 (48)	<0.001	162 (35)	293 (62)	<0.001
Wheeze (%)	451 (29)	435 (46)	<0.001	152 (32)	283 (60)	<0.001
Required antibiotics or steroids for their chest previous 12 months (%)	231 (15)	271 (29)	<0.001	64 (14)	207 (44)	<0.001
MRC dyspnoea score (%)						
1	1148 (73)	632 (67)	<0.001	365 (78)	267 (56)	<0.001
2	305 (19)	186 (20)		83 (18)	103 (22)	
3	88 (6)	74 (8)		17 (4)	57 (12)	
4	40 (3)	50 (5)		4 (1)	46 (10)	
5	0	2		0	2 (0.4)	
Education (%)						
Below O level	922 (58)	631 (67)	<0.001	293 (63)	338 (71)	0.013
O level	342 (22)	169 (18)		94 (20)	75 (16)	
A level	66 (4)	38 (4)		19 (4)	10 (4)	
Some Uni	150 (10)	63 (7)		38 (8)	25 (5)	
Uni degree	58 (4)	33 (4)		16 (3)	17 (4)	
Postgrad	43 (3)	10 (1)		9 (2)	1 (0.2)	
Spirometry ±SD						
FEV ₁ (L)	2.6±0.7	1.9±0.7	<0.001	2.1±0.7	1.7±0.6	0.513
% pred FEV ₁	99±21	76±24	<0.001	83±23	69±24	0.252
FVC (L)	3.3±1.0	3.2±1.0	<0.001	3.4±1.1	2.9±0.9	<0.001
% pred FVC	104±23	101±28	0.003	106±27	95±27	<0.001
FEV ₁ /FVC	77±5	60±9	<0.001	63±8	58±9	<0.001
Mean PLCO _{M2012} score ±SD	2.0±2.6	4.8±4.7	<0.001	3.1±3.0	6.4±5.5	<0.001
Had baseline LDCT (%)	678 (43)	696 (74)	<0.001	303 (65)	413 (87)	<0.001
Emphysema on CT (%)	347 (51)	529 (76)	<0.001	195 (65)	334 (84)	<0.001
Lung cancer (%)*	21 (3.1)	40 (5.7)	<0.001	7 (1.5)	33 (6.9)	<0.001

*Calculated as a percentage of those who had a screening low-dose CT (LDCT) scan at baseline.

A level, advanced level, typically taken by older school pupils prior to college or university, aged 16–18; IMD, index of multiple deprivation; MRC, Medical Research Council; O level, ordinary level, typically taken by school pupils aged 14–16 prior to the year 1988; PLCO_{M2012}, Prostate, Lung, Colorectal and Ovarian Study Risk Prediction Model, 2012 Version.

RESULTS

Spirometry

Of 2541 individuals who attended an LHC, 99.4% successfully performed spirometry (n=2525/2541). Of these 37.4% (n=944) had evidence of airflow obstruction. A comparison of baseline characteristics between those with and without airflow obstruction is detailed in table 1. Those with airflow obstruction had greater tobacco smoke exposure (smoking duration 40±13 vs 31±15 years; p<0.001), were more likely to be current smokers (49% vs 27%; p<0.001), were more symptomatic (68% vs 55%; p<0.001) and had a lower median IMD deprivation rank (2806 vs 2908; p=0.004). Mean predicted FEV₁ was 99%±21% (2.6±0.7 L) in those without and 76%±24% (1.9±0.7 L) in those with airflow obstruction and the corresponding FEV₁/FVC ratio was 0.77±0.05 and 0.60±0.09, respectively (p<0.001).

Participants were asked, as part of the LHC, to self-report whether they had ever been diagnosed with COPD as this is a variable used in the PLCO_{M2012} model to calculate lung cancer risk. Twelve per cent (n=193) of those without airflow obstruction reported a previous diagnosis of COPD and 61% (n=576/944) with airflow obstruction reported no prior diagnosis

of COPD. If we assume a direct relationship between airflow obstruction and COPD, then up to 30.5% (n=769/2525) of LHC attendees may have been misclassified. This varied from 22.7% in those not eligible for screening (n=251/1108) to 36.6% in those who were eligible (n=518/1417).

Previous diagnosis of COPD

A primary care medical case record review was undertaken in all those with airflow obstruction (n=944) to look for evidence of a prior diagnosis of COPD. In just over half of individuals, a diagnosis of COPD was documented (50.3%; n=475; figure 1). All individuals with obstructive spirometry were divided into two groups, those with a documented history of COPD and those without in order to identify characteristics associated with a missed COPD diagnosis. The presence of airflow obstruction without a prior COPD diagnosis was associated, after multivariate analysis, with younger age (p=0.015), male sex (OR_{adj} 1.84, 95%CI 1.37 to 2.47; p<0.0001), lower smoking duration (p<0.0001), mean cigarettes per day (p=0.035), being asymptomatic (OR_{adj} 4.19, 95%CI 2.95 to 5.95; p<0.0001) and higher FEV₁/FVC ratio (p<0.0001; table 2).

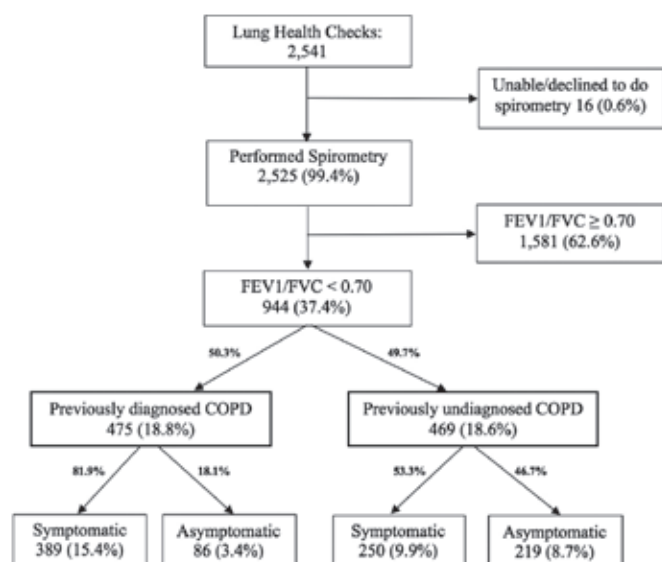


Figure 1 Consolidated Standards of Reporting Trials diagram showing flow of participants through study.

CT finding of emphysema

1374 (54.4%) of those who performed spirometry were eligible for and underwent LDCT screening. The prevalence of radiological emphysema was high, with emphysema detected in 63.4% ($n=876$) of individuals; this increased to 76.0% ($n=529/696$) in those with airflow obstruction compared with 51.2% ($n=347/678$) in those without ($p<0.001$). The detection of emphysema was higher in those with airflow obstruction and a previous diagnosis of COPD compared with those with airflow obstruction and no previous diagnosis of COPD (83.9% vs 65.4%; $p<0.001$).

Screen detected lung cancers

In those with evidence of airflow obstruction, participants previously diagnosed with COPD had a higher mean lung cancer risk score than those without (mean PLCO_{M2012} score $6.4\pm5.5\%$ vs $3.0\pm3.1\%$; $p<0.001$; table 1). A total of 61 lung cancers were detected in the screened population. Within the 2 years of follow-up, 12 participants had died and 61 (4.9%) did not attend their second round scan, none of whom had a diagnosis of lung cancer on ICD code searches. Lung cancer detection was significantly higher in those with airflow obstruction (5.7% vs 3.1%; $p<0.001$; table 1). However, airflow obstruction was not independently predictive of lung cancer, when adjusted for PLCO_{M2012} lung cancer risk score ($p=0.29$).

Among participants with airflow obstruction, lung cancer detection was also significantly higher in those with a COPD

diagnosis compared with those with previously unrecognised airflow obstruction (6.9% vs 1.5%; $p<0.001$; table 1). The risk of lung cancer was significantly higher in those with diagnosed COPD (OR 3.76, 95%CI 1.64 to 8.62; $p=0.002$) and this remained significant after adjustment for PLCO_{M2012} risk score ($_{adj}$ OR 2.80, 95%CI 1.60 to 8.42; $p=0.002$).

DISCUSSION

In this study, we investigated the role of spirometry in a community-based lung cancer screening programme. Airflow obstruction, a key requirement for the diagnosis of COPD, was found in more than a third of participants (37.4%). Half of these individuals had no previous diagnosis of COPD, equivalent to one in five (18.6%) of all LHC attendees. Although those without a prior diagnosis of COPD were less symptomatic than those known to have COPD, the prevalence of symptoms was still high, present in more than half (53.3%). As a consequence, 1 in 10 (9.9%) screening attendees were symptomatic with previously unrecognised airflow obstruction, raising the possibility of COPD. A further 8.7% were asymptomatic but had airflow obstruction. Both groups have increased morbidity and, in the case of symptomatic undiagnosed COPD, increased mortality.⁷ In those with evidence of obstructive spirometry, individuals were less likely to be diagnosed with COPD if they were male, younger, had less tobacco smoke exposure, were asymptomatic and had better lung function.

Our study demonstrates a high prevalence of undetected airflow obstruction among lung cancer screening participants. This is in keeping with previous studies^{14–16}; however, populations recruited to large research trials are generally more educated and of higher SES than would be expected in those at high risk of lung cancer more broadly.^{20,21} Attendees of Manchester's LHCs were from highly deprived areas and may therefore represent a more 'real-world' population not previously captured. We believe that this makes our results highly pertinent to screening implementation. The findings emphasise that COPD and lung cancer coexist and that future lung cancer risk prediction would benefit from more precise COPD diagnosis in primary care. Our study also adds to the pre-existing literature which has examined factors associated with undiagnosed COPD. Consistent with previous large studies, we demonstrate being male, less symptomatic and with better lung function to be associated with having undiagnosed COPD.^{7,8} However, in contrast to Çolak et al⁷ and Martinez et al,⁸ we report being a former smoker to be associated with undiagnosed COPD as well. Case finding programmes targeting current and ex-smokers have had only limited impact^{29,30} and therefore incorporating COPD diagnosis into an LHC-based lung cancer screening programme may improve reach to target populations. Interestingly, we report an almost threefold increased risk of screen detected lung cancer

Table 2 Univariate and multivariate analysis of the association between various clinical measures and the presence of airflow obstruction without a prior diagnosis of COPD

Variable	OR	Univariate 95%CI	P value	OR	Multivariate 95%CI	P value
Age (years)	0.96	0.94 to 0.99	0.003	0.96	0.94 to 0.99	0.015
Sex (F*/M)	1.35	1.04 to 1.74	0.023	1.84	1.37 to 2.47	<0.0001
Smoking status (current* vs former)	1.32	1.03 to 1.71	0.031	1.18	0.82 to 1.71	0.38
Smoking duration	0.97	0.96 to 0.98	<0.0001	0.97	0.96 to 0.99	<0.0001
Cigs/day	0.99	0.98 to 1.00	0.01	0.99	0.98 to 0.99	0.035
Symptomatic (yes* vs no)	4.64	3.35 to 6.43	<0.0001	4.19	2.95 to 5.95	<0.0001
FEV ₁ /FVC	1.07	1.05 to 1.09	<0.0001	1.06	1.04 to 1.08	<0.0001
Education (less than 'O' level* vs 'O' level or greater)	1.48	1.13 to 1.95	0.005	1.28	0.94 to 1.74	0.12
Median IMD rank (below* vs above median)	1.13	0.87 to 1.45	0.36	-	-	-

*Reference measure.

IMD, Index of Multiple Deprivation.

in those with airflow obstruction previously diagnosed with COPD compared with those without a COPD diagnosis. The exact reasons for this are unclear but could possibly be related to the higher levels of smoking exposure, higher degrees of airflow obstruction and higher prevalence of radiological emphysema in this group, all of which have been shown to have an effect on the significance of the impact of COPD on lung cancer risk.³¹

Emphysema was highly prevalent in our screened cohort with evidence of emphysema in two-thirds (63.4%) of individuals. The presence of emphysema was not associated with screen detected lung cancer but was more common in individuals with airflow obstruction (76%). Individuals with obstructive spirometry and emphysema on CT were 2.5 times more likely to have had a previous diagnosis of COPD than those without emphysema.

The Manchester screening pilot is one of the first programmes to use an LHC approach to identify high-risk individuals for LDCT lung cancer screening. Participants of the programme had a median deprivation rank within the lowest decile for England suggesting successful engagement with high-risk individuals of lower SES. The incorporation of spirometry into the LHC was straightforward and identified a large number of people with previously undetected airflow obstruction. We acknowledge that results are based on prebronchodilator spirometry readings at a single timepoint which is not optimal for COPD assessment as this may include individuals with reversible airflow obstruction (eg, asthma). Our results may therefore overestimate the number of undiagnosed COPD cases. We did not label participants as having COPD but communicated the results to primary care with a recommendation for more detailed assessment. Unlike many previous studies that rely on self-reported COPD diagnosis and are therefore subject to recall bias, the use of GP medical records allowed for a more accurate recording of previous COPD diagnosis, allowing for the fact primary care records also have inaccuracies and limitations. This is important as with all survey-based studies there is a reliance on self-reported symptoms, smoking exposure and medical history which may have inherent inaccuracies. In our cohort, for almost one in three attendees, there was discordance between the self-reported presence of COPD and spirometry results. Such inaccuracies can have implications for lung cancer risk prediction models, such as the PLCO_{m2012} used in our study, as participants could be misclassified as high or low risk.

In conclusion, our study demonstrates that a community-based targeted lung cancer screening programme can successfully incorporate spirometry and identify a significant number of individuals with previously unrecognised airflow obstruction, both symptomatic and asymptomatic. Our LHC approach was successful in reaching individuals with low SES from deprived areas and may therefore provide an opportunity to address a significant cause of morbidity and mortality in high-risk populations. Currently, there is a lack of evidence to support screening for COPD in asymptomatic individuals.¹⁰ However, early diagnosis can allow an opportunity for a number of beneficial interventions such as smoking cessation, education, vaccination, exercise and rehabilitation, aggressive management of comorbidities as well as pharmacotherapy which could lead to better outcomes and improved quality of life in these individuals.⁴ In addition to the health benefits associated with this approach, there is also the potential to improve cost effectiveness of such a screening programme especially if combined with other targeted initiatives such as screening for cardiovascular disease³² and smoking cessation.³³ The true benefits of incorporating COPD diagnosis into lung cancer screening services, especially in asymptomatic individuals, are therefore an important question for future programmes to address.

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Acknowledgements JV and Pac are supported by the nihr Manchester Biomedical research centre.

Contributors Service concept: rB, Pac, PVB and JT. service development by members of the Macmillan cancer improvement Partnership: rB, Pac, PVB, JT, Dc, Pe and sT. service operation and delivery by the Manchester University nhs Foundation Trust lung cancer team: hB, Me, rB, Pac and as. radiology reporting by the radiology consortium: rD, Mg, Jh, Ki, DK, sM, Tn, rs, as, es, BT, aW and JW. Data collection, analysis and drafting of manuscript: hB, Jh, JV, rB and Pac. guarantors of overall content: hB, rB and Pac. review, revision and agreement of final manuscript: all authors. Funding The submitted work is cofinanced by the Ministry of Economic Affairs and Climate Policy by means of the PPP. AF was supported by a junior longfond grant (4.2.16.132JO).

Funding This study was funded by Macmillan cancer improvement Partnership.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval clinical data from the screening service were recorded on an ethically approved database (ref rec: 16/nw/0013). north West-greater Manchester West research ethics committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request

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Inibição de mastócitos: um novo mecanismo através do qual nintedanib pode provocar efeitos anti-fibróticos

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2019-214000>).

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Received 11 June 2019

Revised 14 February 2020

Accepted 17 February 2020

Published Online First

24 March 2020

RESUMO

Contexto A fibrose pulmonar idiopática (FPI) é uma doença pulmonar crônica e progressiva que apresenta um prognóstico grave para os doentes diagnosticados. Nintedanib (um inibidor triplo da tirosina quinase) e pirfenidona (mecanismo de ação pouco claro) são as únicas terapias aprovadas para a FPI, apresentando, no entanto, uma eficácia limitada. Os mecanismos patogênicos desta doença não estão totalmente esclarecidos. Contudo, foi postulado um papel para os mastócitos (MCs).

Objetivos O objetivo deste trabalho foi investigar um papel para os MCs na FPI e compreender se nintedanib ou pirfenidona poderiam ter impacto na função dos MCs.

Métodos e resultados Os MCs apresentaram-se significativamente elevados num pulmão humano com FPI e negativamente correlacionados com a função pulmonar inicial (FVC). É importante referir que os MCs se apresentaram positivamente associados ao número de focos de fibroblastos, o que pode estar associado ao aumento de mortalidade. Adicionalmente, os MCs encontravam-se aumentados na região circundante junto aos focos de fibroblastos e estudos de co-cultura confirmaram um papel na comunicação cruzada entre MCs e fibroblastos na fibrose. O nintedanib, ao contrário da pirfenidona, inibiu a sobrevivência de MCs induzida pelo fator de células estaminais recombinantes (SCF). Uma avaliação adicional de nintedanib determinou que este também inibiu a sobrevivência de MCs mediada por fibroblastos humanos. Provavelmente, tal ocorreu através de um efeito direto no ckit (receptor SCF), uma vez que nintedanib bloqueou a fosforilação do ckit estimulada por SCF, bem como os efeitos a jusante sobre a proliferação de MCs e a libertação de citocinas. Adicionalmente, o nintedanib atenuou o aumento de MCs pulmonares e teve impacto na frequência elevada de densidade tecidual (HDFm) em modelo de bleomicina em rato com fibrose pulmonar.

Conclusão O nintedanib inibe a sobrevivência e ativação dos MCs, proporcionando assim um novo mecanismo adicional através do qual este medicamento pode exercer efeitos anti-fibróticos em doentes com FPI.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive and ultimately fatal lung disease with unknown aetiology and increasing incidence.¹ While still incompletely understood, the pathogenesis of IPF is thought to involve recurrent injury to the alveolar epithelium inducing an aberrant wound healing response, characterised by activation and proliferation of fibroblasts and myofibroblasts.² Formation of the fibroblastic foci, as well as the deposition of extracellular matrix (ECM) are downstream pathological fea-

Mensagens-chave

What is the key question?

► Do mast cells (MCs) correlate with idiopathic pulmonary fibrosis (IPF) disease activity, and can either nintedanib or pirfenidone modulate MC survival or activation?

What is the bottom line?

► MCs are increased in IPF lung and negatively correlate with baseline lung function (FVC) and positively correlate with the number of fibroblast foci. Nintedanib, but not pirfenidone, can inhibit human MC survival and activation in vitro and MC recruitment in the rat bleomycin model.

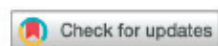
Why read on?

► Inhibition of MC survival or activation may be a novel additional mechanism by which nintedanib exerts anti-fibrotic effects in patients with IPF.

tures³ that result in an abnormal lung structure referred to as the characteristic 'honeycombing' morphology, which is associated with impaired lung function.⁴ The role of structural cells such as fibroblasts in the pathogenesis of fibrosis is well accepted; however, less understood is the contribution of immune cells which are also present in IPF lung.⁵⁻⁹ The mast cell (MC) is an innate immune cell well known for its involvement in allergy, asthma and in host defence against parasites.^{10 11} However, MCs are also a key cell responding to tissue injury and are found very early at the site of the wound.¹² On activation, MCs can release an array of mediators, which have been shown to partake in all stages of the wound healing process, including inflammation, proliferation and re-modelling.¹³ Thus, given the dysregulated nature of repair in IPF, this cell could be a potential pathogenic link to this disease.

MCs have been postulated to be pro-fibrotic in IPF, although the data are conflicting and their role remains controversial. Several studies have shown that MCs and their mediators, such as histamine, are increased in lung tissue and bronchoalveolar lavage from patients with IPF.¹⁴⁻²⁰ Mechanistically, reports have demonstrated that human lung fibroblast and MC crosstalk leads to increased MC activation and survival, as well as fibroblast proliferation.¹⁷

Others have suggested that the MC mediators tryptase, chymase and histamine induce both lung and skin fibroblast proliferation and



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Para citar: Overed-Sayer C, Miranda e, Dunmore R, *et al.* Thorax 2020;75:754-763.

collagen production,^{19,21–23} and Shimbori and colleagues recently demonstrated that stretch-induced degranulating MCs activate the pro-fibrotic cytokine TGF- β 1.²⁰ Andersson and colleagues provide evidence for a switch to the connective tissue MC subtype expressing both chymase and tryptase proteases (MCTC) in IPF lung,²⁴ and this increase in MCTCs in IPF has been confirmed recently.²⁰ In contrast, Cha and colleagues propose a protective role for lung MCs since patients with higher numbers of these cells had less decline in lung function.¹⁶

Stem cell factor (SCF) is a key survival factor for mast cells, acting through the tyrosine kinase receptor ckit (also known as CD117 or SCF receptor). Importantly, a phase II clinical trial with a ckit inhibitor Imatinib (Gleevec) had no significant effect on lung function decline (or mortality), although the effect on MCs was not determined in this study.²⁵

Recently, two small molecule drugs, pirfenidone and nintedanib, were licensed for IPF following successful phase III clinical trials demonstrating a slowing in lung function decline.^{26–28} Pirfenidone is a small molecule whose precise target is unknown, that exerts effects on transforming growth factor (TGF)- β 1 signalling and PDGF as well as acting as an antioxidant,²⁹ whereas nintedanib is a broad tyrosine kinase inhibitor with known activity on platelet-derived growth factor (PDGF), fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) receptors.³⁰ Thus, it is plausible that nintedanib may also have activity against the ckit receptor, which is found on MCs. Notably, the effects of nintedanib or pirfenidone on MC survival and function have not yet been investigated.

In this study, we sought to confirm that MCs are increased in IPF versus non-diseased lung, and compared MC density in other fibrotic lung diseases such as chronic hypersensitivity pneumonitis (HP) and non-specific interstitial pneumonia (NSIP). We also assessed MCs for pro-fibrotic functions. Furthermore, we investigated whether nintedanib or pirfenidone could impact MC survival, and therefore whether this could be an additional novel mechanism explaining why these small molecules are efficacious in IPF.

MATERIALS AND METHODS

See online supplementary for a more detailed version of these methods.

MC quantification and phenotyping

Formalin-fixed paraffin-embedded (FFPE) sections from lung biopsy specimens from patients with IPF (n=17), chronic HP (n=9) and NSIP (n=9) and normal adjacent lung specimens taken from patients with lung cancer (normals; n=20) were obtained from Royal Papworth Hospital Research Tissue Bank. Patients gave written consent and the study was approved by NRES Committee East of England—Cambridge East via Royal Papworth Hospital Research Tissue Bank generic ethical approval.

Consecutive 3 μ m sections of the FFPE samples were stained for H&E or dual immunohistochemical staining for chymase and tryptase (Ventana Discovery Ultra; Roche). Tissue area was calculated by subtraction of white space from the total lung section area. MCs were analysed per area of lung section and per area of tissue. Fibroblastic foci, established fibrosis and nonfibrotic areas of the IPF lung sections were annotated by a registered senior pathologist (online supplementary figure S1), and the MC populations quantified. Subsequently, the outer edge of the foci was extended by 500 μ m and MCs in the surrounding area were quantified. See online supplementary methods for more details.

MC protease signature analysis in IPF lung

Additional lung tissue was obtained from patients with IPF (n=10) undergoing lung volume reduction surgery or lung transplantation at Temple University Lung Center as part of a separate study. Patients gave written consent and the study was

approved by the institutional review board at Temple University Lung Center. Normal lung tissue samples (n=9) were obtained from the National Disease Research Interchange (NDRI), in accordance with local internal review board ethical approval. Microarray analysis was performed using Affymetrix HG-U133Plus 2.0 microarrays. For more information, see online supplementary methods.

Cell culture and in vitro assays

Cord blood-derived MCs (CBMCs) were differentiated from CD133+ cord blood precursors (Lonza). These cells are predominantly of the MCT phenotype (approximately 70%), as determined using a similar staining protocol to that used to phenotype the lung tissue MCs. Conditioned media was prepared from CBMCs that had been cultured for 7 days. CBMC lysates were prepared by sonication and freeze thawing. See online supplementary methods for details.

CBMC survival

CBMCs were cultured with recombinant SCF (MedImmune, see online supplementary methods for details) in the presence or absence of nintedanib, pirfenidone (both Selleckchem.com) or DMSO vehicle (Sigma Aldrich). After 7 days, CBMCs were stained with a viability dye and anti-ckit mIgG1 APC (BD Pharmingen) and the number of viable ckit-positive MCs in a fixed volume was counted in a flow cytometer (LSRII Fortessa) and compared with control.

CBMC proliferation, CCL2 release and phosphorylation of ckit

CBMCs were stimulated with recombinant SCF (MedImmune) in the presence or absence of nintedanib (LC Laboratories), DMSO vehicle, anti-SCF pAb (AF-255-NA) or goat IgG isotype (both antibodies R&D Systems). Phosphorylation of ckit was measured using an electrochemiluminescence-based phospho-ckit assay (MesoScale Discovery) after a 10min stimulation and CBMC proliferation was measured by 3H-thymidine incorporation after a 3-day stimulation. CCL2 was measured in culture supernatants by MSD (MesoScale Discovery). See online supplementary methods for details.

CBMC:NHLF co-culture and flow cytometry assessment of MC and fibroblast numbers

Normal human lung fibroblasts (NHLFs) and CBMCs were cultured alone or co-cultured at a 1:1 ratio in media containing anti-SCF, goat IgG isotype control (67nM; both R&D Systems), nintedanib (30nM; LC Laboratories), DMSO vehicle or media alone over a time course up to 21 days. At each time point, cells were stained with a viability dye and anti-ckit APC mIgG1 and the number of ckit-positive (MCs) and ckit-negative viable cells (NHLFs) in a fixed volume was counted in a flow cytometer (LSRII Fortessa). See online supplementary methods for more details.

Fibroblast stimulation

NHLFs were stimulated with recombinant human bFGF in the presence of nintedanib (LC Laboratories), pirfenidone (Selleckchem.com), or DMSO vehicle for 48hours or for 48–72hours with MC lysates, conditioned media or MCs at a ratio of 1:1. TGF- β 1 (R&D Systems) was included as a positive control for a smooth muscle actin (α SMA) experiments. Proliferation was assessed by 3H-thymidine incorporation. α SMA expression was assessed by immunofluorescence following a 72-hour stimulation.

Animal studies

Rats (male CD, 6–8 weeks old) received 0.9 U/kg bleomycin sulphate (Bleo-Kyowa) or saline (1 mL/kg) intratracheally under iso-flurane anaesthesia (study day 0). Nintedanib (LC Laboratories)

was dosed at 60 mg/kg daily by oral gavage, from day 0 to day 13. Changes in MC number and fibrosis markers were assessed on day 14. Animal housing and procedures were approved by the local ethical committees (The Babraham Institute, UK) in accordance with institutional and the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines (see online supplementary methods for more details). Sections were stained using H&E and Giemsa for MC quantification, HE alone or Masson's trichrome (MTC) for collagen using standard protocols (Damsgaard; Leica Autostainer). HE and MTC scanned images were analysed by Biocellvia using their IPF assay based on assessment of parenchymal tissue density using a proprietary software program. The high tissue density frequency (HDFm) was calculated to specifically quantify fibrotic tissue in lung parenchyma. The proportion of collagen staining by MTC was measured using standard image analysis methods (see³¹ for validation of this method and online supplementary for more details).

Statistical analysis

Details of the sample size and statistical analysis performed can be found in the relevant figure legend. Two group comparisons were carried out by t-test for normally distributed data or Mann-Whitney U non-parametric test. Multiple group comparisons were assessed by one-way analysis of variance (ANOVA) with Sidak's post hoc multiple comparisons for normally distributed data, or where assumptions of normality or homogeneity of variance were not valid, by Kruskal-Wallis with Dunn's post hoc multiple comparisons test. Analysis of MCs in different regions of the lung within the same patient was assessed by repeated measures ANOVA with Geisser-Greenhouse correction (for assumption of sphericity) with Sidak's multiple comparisons. Correlations were assessed by Pearson's correlation or nonparametric Spearman's correlation. All analyses and plots were generated in GraphPad Prism, and a p value of less than 0.05 was considered statistically significant.

RESULTS

MCs are significantly elevated in IPF lung

We sought to determine the number, phenotype and localisation of MCs in the lungs of patients with IPF (n=17) and compared this with MCs in non-diseased lung taken from age-matched patients undergoing cancer resections (normals; n=20). We also examined whether MCs are elevated across other fibrotic lung conditions in samples taken from nine patients with chronic HP and nine patients with NSIP (table 1). We found that the number of MCs per area of lung were significantly increased in both IPF and HP lung samples. In contrast, MC numbers were not altered in NSIP lung samples when compared with normal (non-fibrotic) controls (figure 1A). Although the control and IPF groups are not matched according to gender, this is unlikely to be responsible for the observed difference in MC density; we observed no significant difference in MC density between males and females in healthy lung (online supplementary figure S2).

Since the fibrotic process involves the deposition of extracellular matrix, leading to increased tissue mass, we measured the

proportion of tissue mass area in the lung sections (by subtracting the air spaces) and found this to be enhanced in IPF lung compared with normal lung (figure 1B). Thus, we employed a more stringent analysis which calculated the MC number per area of tissue to confirm whether MC density was actually elevated, and not simply due to the increase in tissue mass in IPF lung. This analysis was possible due to the use of automated software to subtract the white airspaces. The elevation in MC number in IPF lung remained statistically significant (figure 1C). All further data are expressed as MCs per tissue area unless specified, to account for this increase in tissue area in fibrotic lung.

To determine whether increased MCs resulted in a switch in MC subtypes, staining for MC proteases was performed and chymase, tryptase (MCT) or double-positive (MCTC) MCs (figure 1D) were quantified according to both total area (online supplementary table S1) and tissue area (table 2). The number of chymase+ MCs and double-positive MCTCs were significantly increased in IPF lung compared with nonfibrotic controls, with a similar trend in tryptase+ MCTs (table 2).

MC density is associated with the number of fibroblastic foci and inversely correlates with lung function

Increased fibroblast foci in the lungs of patients with IPF has been shown to predict mortality.^{32,33} Therefore, we examined whether there was an association between MCs and the number of fibroblastic foci in our cohort. Strikingly, we observed a moderately strong and significant positive correlation between the numbers of MCs and fibroblast foci in patients with IPF ($r^2=0.3545$, figure 1E). Furthermore, we also found that MC numbers per area of lung were strongly inversely correlated with lung function (% predicted FVC), that is, patients with lower FVC had increased numbers of lung MCs ($r_s=-0.4616$, figure 1F). Interestingly, a negative trend between MCs per area of tissue and the % predicted FVC was also observed, but this did not reach statistical significance (online supplementary figure S3).

We next examined the localisation of MCs within IPF lung. Areas of apparent normal non-fibrotic parenchyma, fibroblastic foci and established fibrosis were annotated by a trained pathologist. MCs were detectable in all areas of IPF lung, but surprisingly were not increased within the foci themselves. Instead, numbers were significantly elevated within areas of established fibrosis compared with the foci (figure 1G). Knowing that MCs interact with fibroblasts^{17,34-36} and hypothesising that activated, degranulating MCs could impact local fibroblast foci, we quantified the number of MCs immediately surrounding the foci (ie, within a 500 μ m periphery). Strikingly, we found that the MC density was significantly higher in the region surrounding the foci compared with the foci itself, with the highest numbers being identified in areas of established fibrosis (figure 1H).

Increased MC signature and sCF expression in IPF lung

A second cohort from normal (NDRI) and IPF (Temple) donors was obtained to perform microarray gene expression analysis.

Table 1 Demographic and spirometric data at baseline

	Controls (n=20)	IPF (n=17)	Chronic HP (n=9)	NSIP (n=9)	Control vs IPF	Control vs chronic HP	Control vs NSIP
Age, years	70 (63–73) (n=18)	64 (57–71)	60 (48–67)	53 (48–65)	p=0.6313	p=0.0576	p=0.0254
Gender, male/female	8/12	14/3	4/5	2/7	p=0.0176	p>0.9999	p=0.4311
Smoking status, ever/never-smokers	11/4	11/5	3/4	5/3	p>0.9999	p=0.3426	p=0.657
FVC, L	3.2 (2.6–4.3) (n=18)	2.6 (2.5–3.3) (n=16)	1.9 (1.4–2.6) (n=5)	2.0 (1.5–3.1) (n=6)	p=0.372	p=0.0077	p=0.0418
FVC % predicted, %	108.5 (103.5–118.3)	77.0 (65.8–95.0)	58.7 (41.0–70.8)	77.0 (60.2–91.2)	p=0.0009	p=0.0001	p=0.0057
DLCO, mL/min/mm Hg	6.3 (5.5–7.4) (n=17)	4.2 (3.4–5.4) (n=14)	4.2 (2.1–4.2) (n=5)	4.2 (3.3–4.6) (n=5)	p=0.0021	p=0.0009	p=0.0127
DLCO % predicted, %	80.0 (72.0–88.5)	54.5 (45.5–62.0)	55.0 (22.7–55.6)	56.4 (43.6–57.2)	p=0.0002	p=0.0003	p=0.0039
Steroid use at baseline yes/no	3/11	1/14	3/3	3/3	p=0.3295	p=0.3027	p=0.3027

Data expressed as median (IQR) unless specified. Age is recorded at time of diagnosis apart from controls whose age is captured at the time of baseline measurements. Groups compared by Kruskal-Wallis test with Dunn's post hoc test for continuous variables, and by Fisher's exact test for categorical variables.

DLCO, diffusing capacity for carbon monoxide; HP, hypersensitivity pneumonitis; IPF, idiopathic pulmonary fibrosis; n, number of available data; NSIP, non-specific interstitial pneumonia.

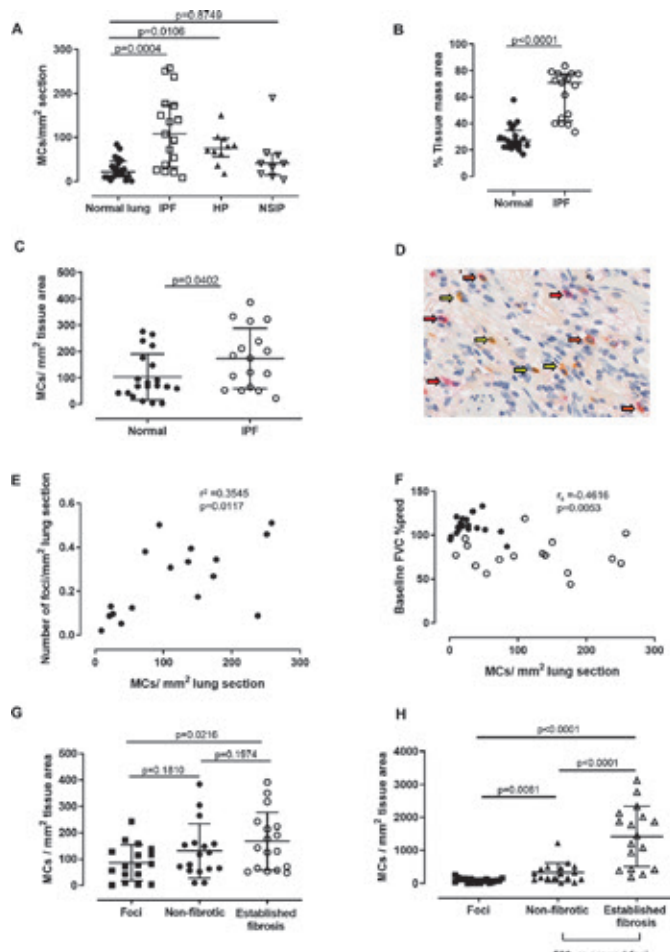


Figure 1 Increased mast cells (MCs) in idiopathic pulmonary fibrosis (IPF) are associated with a higher number of fibroblastic foci. (A) The number of MCs/mm² lung section is significantly higher in patients with IPF (n=17) compared with normals (n=20). HP, hypersensitivity pneumonitis (n=9); NSIP, non-specific interstitial pneumonia (n=9). (B) The proportion of lung section that is tissue (vs airspace) is higher in patients with IPF. (C) The number of MCs/mm² tissue is higher in IPF than normal lung. (D) Representative image of lung. Arrows point to tryptase MCT (red), chymase (yellow) and dual positive MCTC cells (orange). (E) The number of MCs per area lung is positively correlated with the number of fibroblast foci per area lung. (F) There is a negative correlation between the number of MCs/area lung section and the baseline FVC. Closed circles, normals; open circles, IPF. (G) Distribution of MCs across IPF lung. MCs are no higher within the foci than other regions. (H) MCs are higher in the 500 µm region surrounding the foci. Details of the statistical tests used: (A) Kruskal-Wallis with Dunn's multiple comparison, (B) Mann-Whitney U test, (C) unpaired t-test, (E) Pearson's correlation, (F) Spearman's correlation and (G and H) repeated measures ANOVA with Geisser-Greenhouse correction (for assumption of sphericity) with Sidak's multiple comparisons. Median and IQR plotted for non-parametric data and mean and SD for parametric data.

To confirm MC presence, we applied a MC-specific signature, composed of three MC protease genes: *cpa3*, *TPSB2* and *TPSAB1* (encoding carboxypeptidase 3, tryptase beta-2 and tryptase alpha/beta 1, respectively) to the analysis. This signature was markedly elevated in IPF compared with normal lung (figure 2A). Furthermore, we observed increased expression of SCF (the key MC survival factor) in IPF lung (figure 2B).

MCs induce fibroblast proliferation and activation

We sought to confirm and extend previous findings that an increased MC presence may drive the fibrotic pathology.^{19 21–23 37} When NHLFs were cultured in the presence of MC conditioned media (media cultured with MCs for 7 days) (figure 3A) or resting MC lysates (figure 3B), a significantly enhanced NHLF proliferation was observed. A similar effect was also seen when IPF fibroblasts were stimulated with MC conditioned media (online supplementary figure S4a) and when we substituted the conditioned media

Table 2 MC subtypes in IPF vs non-fibrotic lungs (number of MCs/mm² tissue area)

	Non-fibrotic lung (n=20); number of MCs/mm ² tissue area	IPF (n=17); number of MCs/mm ² tissue area	P value
Chymase only	3 (0–39)	13 (4–53)	0.0003
Tryptase only (MCT)	65.5 (1–271)	122 (5–374)	0.0894
Chymase+ tryptase (MC _{TC})	1 (0–64)	3 (1–37)	0.0284

Median and range shown. Groups compared by Mann-Whitney U test. IPF, idiopathic pulmonary fibrosis; MC, mast cell.

for recombinant MC mediators (tryptase, chymase, histamine, PDGF-AA; online supplementary figure S4b). Since these MC mediators induce fibroblast activation and subsequent differentiation into myofibroblasts,³⁸ we performed MC–fibroblast co-culture experiments to investigate the effects of MCs on fibroblast activation. Co-culture for 72 hours led to significantly enhanced numbers of high intensity α smooth muscle actin (α SMA)–expressing cells; an increase was also seen following TGF- β stimulation (the positive control, representative images, figure 3C). Similarly, MC conditioned media induced more high intensity α SMA expres-

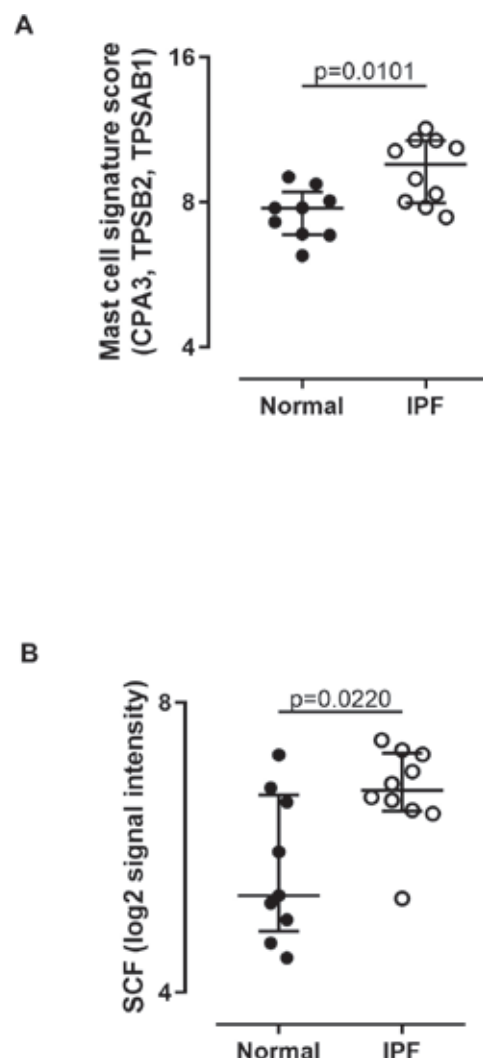


Figure 2 Increased mast cell signature and SCF expression in IPF lung. (A) Increased expression of mRNA encoding three MC protease genes and (B) SCF in lung of patients with IPF undergoing lung volume reduction surgery or lung transplantation (n=10) compared with normal lung tissue samples (n=9). CPA3, TPSB2 and TPSAB1 were among the strongest differentially expressed transcripts using a moderated t-test and Benjamini-Hochberg correction for multiple comparisons. These three genes comprise a MC signature. A signature score was calculated for each patient by summation of the fRNA normalised expression value reported by the microarray for each gene in the signature. The median and IQR for each group is plotted and groups were compared by Mann-Whitney U test. IPF, idiopathic pulmonary fibrosis; MC, mast cell; SCF, stem cell factor.

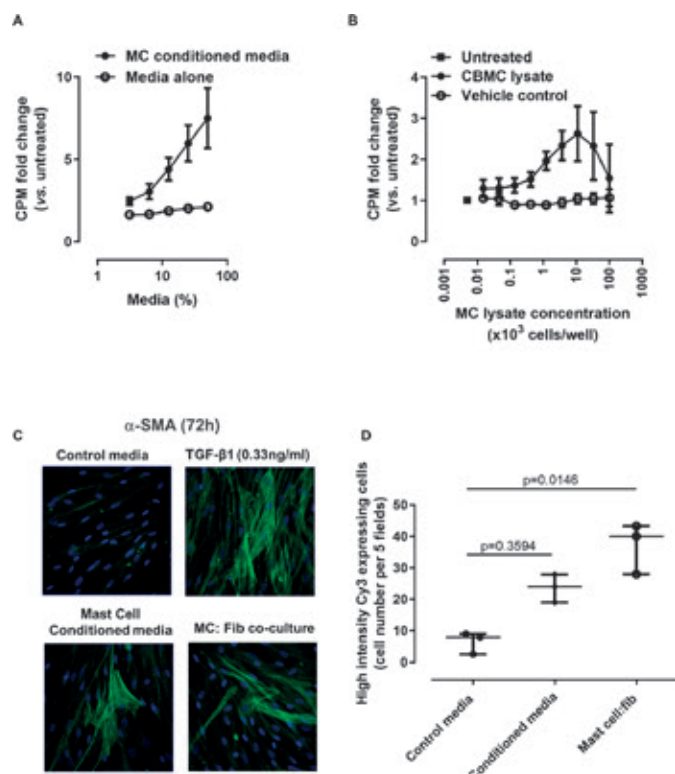


Figure 3 Mast cells (MCs) induce fibroblast proliferation and activation. MCs stimulate fibroblast proliferation, assessed by 3Hthymidine-incorporation assay. Normal human lung fibroblasts (NHLFs) were stimulated for 48 hours with (A) conditioned media obtained from MC culture and (B) MC lysates (2 different MC donors, multiple batches of lysate and conditioned media). Data are mean (SE) for at least three separate experiments, and the fold change compared with untreated cells is plotted. (C) MC conditioned media and co-culture with MCs stimulate α SMA expression in NHLFs. TGF- β 1 stimulation was included as a positive control. Representative images at $\times 40$ magnification for greater resolution. (D) A blinded quantification of high α SMA expressing cells ($\times 20$ magnification, 5 fields/well) in three separate experiments was carried out. Mean values for 3 separate experiments are plotted plus the overall median value and IQR for each condition. Groups were compared by Kruskal-Wallis with Dunn's post hoc test. CBMC, cord blood-derived mast cell; CPM, counts per minute.

sing fibroblasts; however, this did not reach statistical significance (figure 3D). Formation of α SMA fibres by fibroblasts is associated with activation of these cells into a myofibroblast phenotype and thus supports a pro-fibrotic role of MCs on fibroblasts.

Nintedanib but not pirfenidone inhibits NHLF proliferation and MC survival

We next examined whether either of the two current therapies for IPF had an effect on MC survival or activation. Since nintedanib is a tyrosine kinase inhibitor, we hypothesised that it may induce effects downstream of the tyrosine kinase receptor ckit, the receptor for the MC survival factor SCF. Nintedanib significantly inhibited recombinant human bFGF-mediated fibroblast proliferation ($IC_{50}=526$ nM; figure 4A), consistent with previous reports,³⁰ confirming nintedanib's expected activity. Moreover, nintedanib also markedly inhibited recombinant human SCF-mediated MC survival in vitro ($IC_{50}=13.7$ nM; figure 4B). Notably, pirfenidone had no impact on either fibroblast proliferation or MC survival.

Nintedanib inhibits fibroblast-mediated MC survival

Our data suggest that a significant crosstalk exists between MCs and fibroblasts and that this interaction may be required for a pathological role of MCs in IPF. Thus, we employed a MC-fibroblast co-culture system similar to that used by Wygrecka and colleagues,¹⁷ and quantified MC survival via flow cytometry (figure 5A). Here, we confirmed that NHLFs provided an essen-

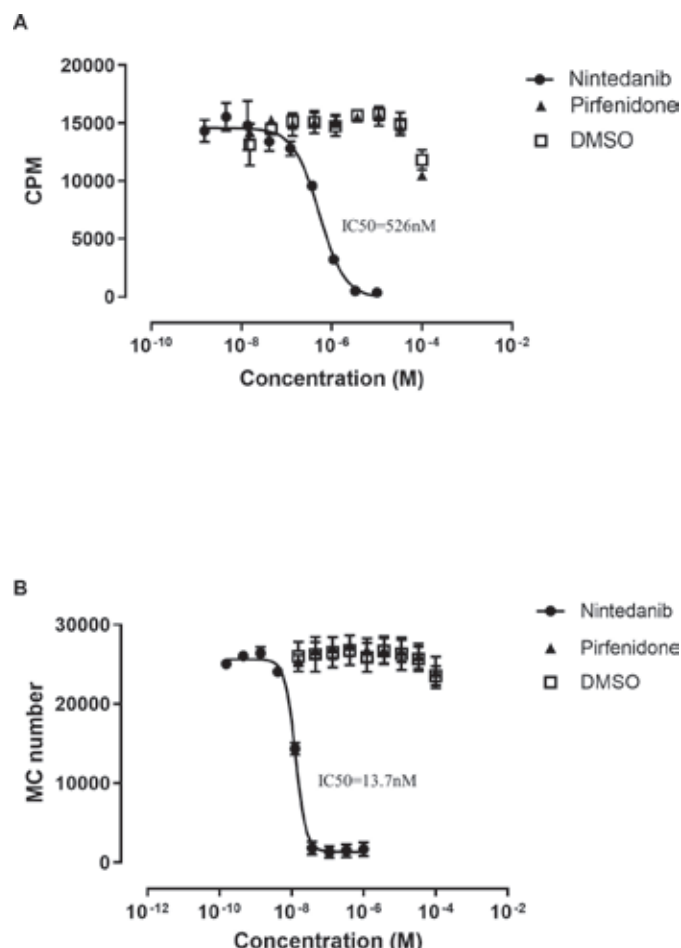


Figure 4 Nintedanib but not pirfenidone inhibits normal human lung fibroblast (NHLF) proliferation and mast cell (MC) survival. (A) Nintedanib inhibited fibroblast proliferation induced by 100pM basic fibroblast growth factor (bFGF). (B) Nintedanib inhibited survival of MCs cultured with 4 nM rhSCF. ckit-positive MCs were quantified by flow cytometry after 7 days of treatment with nintedanib or pirfenidone. DMSO was used as a vehicle control. Data are presented as mean (SE) of three separate experiments. CPM, counts per minute.

tial survival benefit to MCs, whereas in the absence of NHLFs MCs died within 7–14 days (figure 5B). Importantly, nintedanib (30 nM) almost completely ablated this fibroblast-mediated MC survival (84% reduction day 14; figure 5C) and lower concentrations (10 nM) also inhibited survival (online supplementary figure S5). The reduction in survival was similar in magnitude to that observed in the presence of an anti-SCF antibody (82% at day 14; figure 5C). In our co-culture system, no fibroblast proliferation was observed (online supplementary figure S6). However, a potential fibroblast survival benefit was seen when cells were co-cultured with MCs. Nintedanib did not affect fibroblasts alone or the co-culture system. Collectively, these data suggest that nintedanib can inhibit fibroblast-mediated MC survival which is largely dependent on endogenous SCF.

Nintedanib significantly impacts KIT receptor signalling/phosphorylation

We next questioned whether inhibition of ckit receptor activation could be the mechanism by which nintedanib impacts MC survival. Thus, we examined the effect of nintedanib on rhSCF-mediated ckit phosphorylation on MCs. Nintedanib fully inhibited phosphorylation of ckit, which was comparable with the effect observed with anti-SCF, with an IC_{50} in the nanomolar range, and suggesting that inhibition of ckit activation is occurring at biologically relevant concentrations (IC_{50} : 2.5nM vs 13.3nM for anti-SCF and nintedanib, respectively; figure 6A). Nintedanib also significantly inhibited rhSCF-mediated MC proliferation, a downstream effect of ckit receptor activation (IC_{50} : 1.2nM vs

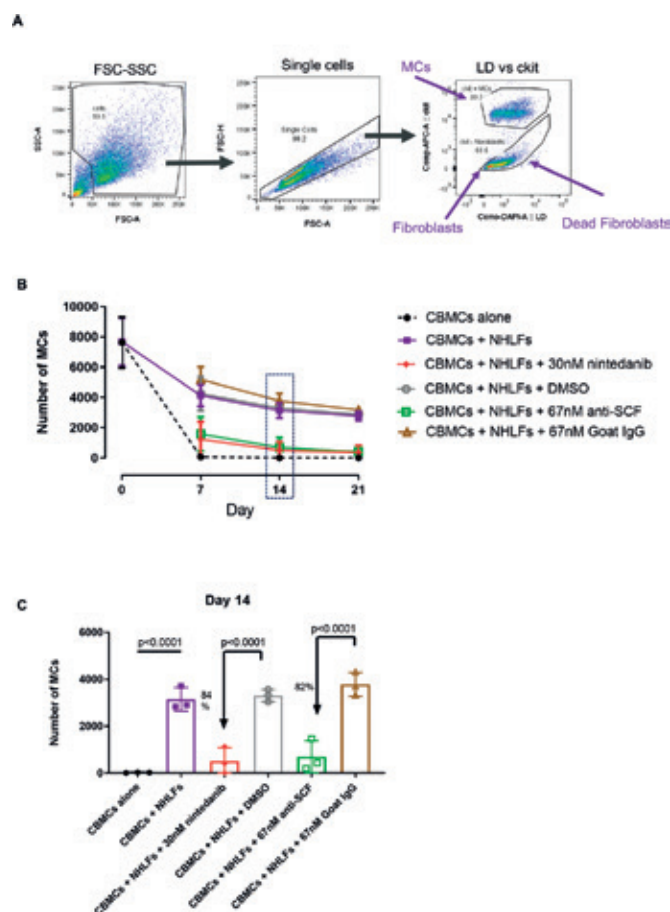


Figure 5 Mast cell (MC) survival in co-culture with fibroblasts is mediated largely through stem cell factor (SCF) and is inhibited by nintedanib. MCs were cultured alone or with normal human lung fibroblasts (NHLFs) in media lacking SCF or IL-6 growth factors for 21 days. (A) At each time point, cells were stained with a viability dye and anti-kit APC mlgG1 and kit-positive MCs quantified by flow cytometry. There is a survival benefit to MCs co-cultured with NHLFs, and this is inhibited in the presence of 67 nM anti-SCF. Inclusion of 30nM nintedanib in the co-culture has a similar effect. Data plotted as mean and SD of 3 separate experiments (2 MC donors). (B) Experimental time course plotted. (C) Day 14 data plotted as bar chart with mean and SD and showing percentage inhibition relative to isotype/vehicle control. Groups were compared by ANOVA with Sidak's post hoc test for multiple comparisons. CBMC, cord blood-derived mast cell; FSC-SSC, forward scatter versus side scatter; LD, live dead viability dye.

14.8nM for anti-SCF and nintedanib, respectively; figure 6B), as well as release of the cytokine CCL2 (IC_{50} : 2.6nM vs 12.2nM for anti-SCF and nintedanib, respectively; figure 6C) which has been associated with MC activation post SCF or IgE stimulation.³⁹ Thus, nintedanib is a potent inhibitor of ckit activation.

Nintedanib reduces MC recruitment in rat bleomycin model

Finally, we employed a bleomycin model to investigate the effect of nintedanib on MCs in vivo. Rats were selected since, like humans, MCs are present in the rat lung parenchyma, whereas lung MCs in mice are sparse and localised predominantly adjacent to upper airways.⁴⁰ Rats were dosed orally with 60mg/kg nintedanib or water (vehicle) daily following a single intratracheal installation of bleomycin (or saline control) (figure 7A) and MC density and fibrotic read-outs were assessed at day 14. Bleomycin induced a marked increase ($p=0.05$) in lung MCs (figure 7B and C), which was ablated with nintedanib treatment in bleomycin dosed rats (figure 7C). Furthermore, we observed a reduction in the levels of histamine in lung homogenates, although this did not reach statistical significance (online supplementary figure S7). Nintedanib also had an impact on the fibrosis endpoints in this model; HDFm, a measure which specifically quantifies fibrotic tissue in lung parenchyma, was significantly decreased

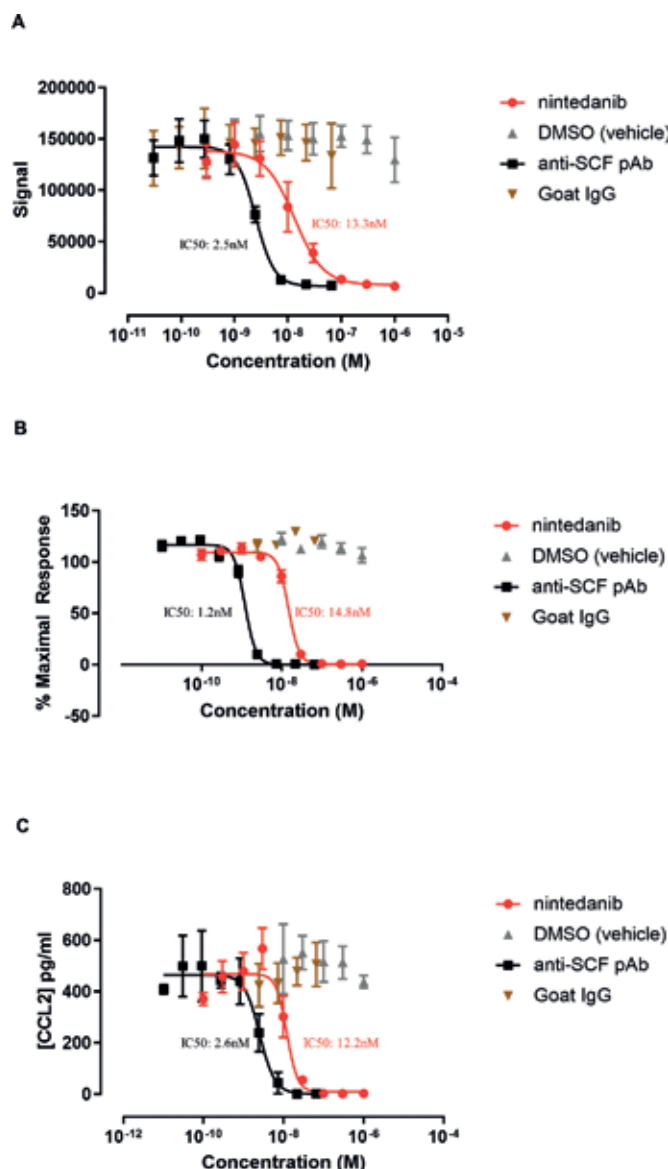


Figure 6 Nintedanib inhibits ckit activation. (A) Nintedanib inhibits phosphorylation of ckit induced by 10 min stimulation with 4 nM rhSCF. IC_{50} : 2.5 nM vs 13.3 nM for anti-SCF and nintedanib, respectively. (B) Nintedanib inhibits mast cell (MC) proliferation induced by stimulation of MCs with 4 nM rhSCF for 3 days. (C) Nintedanib inhibits CCL2 release induced by stimulation of MCs with 4 nM rhSCF for 3 days. Data are plotted as mean (SE) of 3 separate experiments. DMSO was used as a vehicle control and anti-SCF pAb was included as a positive control. CBMC, cord blood-derived mast cell; SCF, stem cell factor.

with nintedanib treatment compared with bleomycin vehicle control (figure 7D,E), and there was a similar effect on mean tissue density (Dm) (online supplementary figure S8). In addition, we observed a trend towards decreased collagen by MTC with nintedanib treatment (figure 7F). The variability in the effects of nintedanib on fibrotic endpoints was likely due to the patchy nature of fibrosis induced by bleomycin since nintedanib had no significant effect on the levels of lung hydroxyproline, or collagen and fibronectin mRNA expression (online supplementary figure S7).

DISCUSSION

In this study, we sought to investigate a role for MCs in the pathogenesis of IPF and to determine whether nintedanib and pirfenidone, the only approved therapies for IPF, had an impact on MC function.

We showed that total MCs were significantly increased in IPF compared with normal lung, which is consistent with studies by others including Cha and colleagues.^{14 16 17 20} The mismatch in gender between the control and IPF groups was not responsible for this difference; there was no difference in MC density according to gender. Importantly, our novel finding of a significant positive

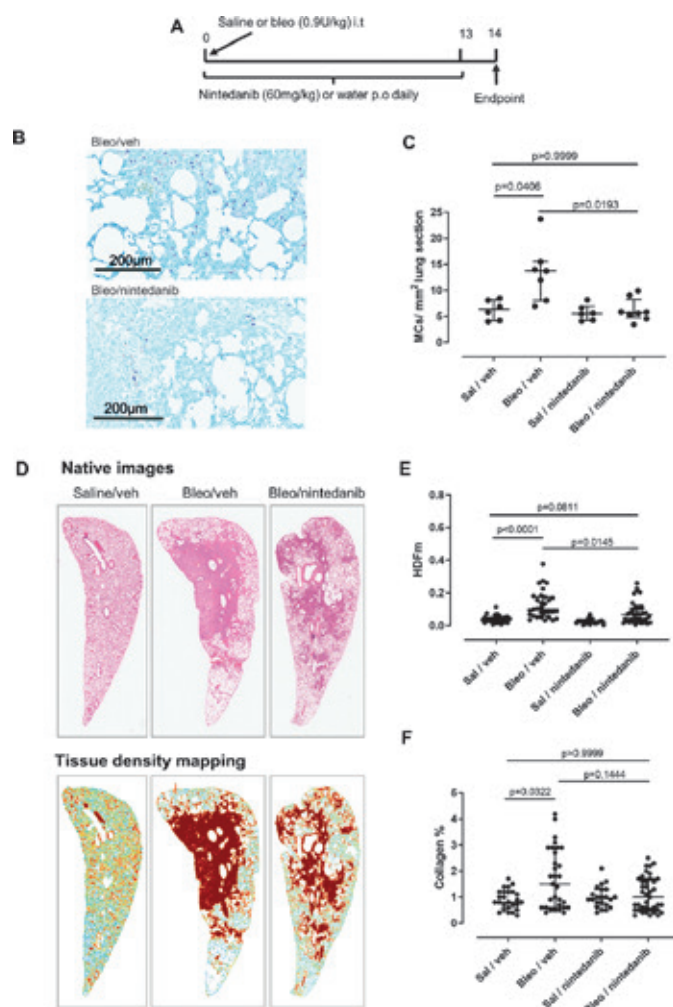


Figure 7 Nintedanib inhibits lung mast cells (MCs) in the rat bleomycin model. (A) Outline of study design. (B) Rat lungs were stained with Giemsa to visualise the MCs. Representative sections from bleomycin-treated animals treated with nintedanib or vehicle are shown. (C) The number of MCs per area lung was increased with bleomycin and was inhibited by nintedanib. (D) Representative images of annotation of tissue density mapping in which high parenchymal tissue densities specifically located in pulmonary foci have been pseudocoloured in brown. (E) There is a significant increase in the HDFm in the lung parenchyma with bleomycin, and this is inhibited by nintedanib treatment (H&E staining, 5 sections per animal; Sal/vehicle n=6, Bleo/vehicle n=7, Bleo/nintedanib n=9, Sal/nintedanib n=5). (F) There was also a trend towards a decrease of collagen content with nintedanib treatment, although this was not statistically significant (Masson's trichrome staining, 5 sections per animal) Kruskal-Wallis H=6.571, p=0.0869. Median and IQR are plotted and groups were compared by Kruskal-Wallis with Dunn's multiple comparisons test.

correlation between the number of MCs versus fibroblast foci in patients with IPF supports an association between MC density and IPF mortality since increased foci are reported predictors of mortality.^{32,33} Of relevance, MC numbers inversely correlated with FVC, a clinical measure of lung function, which may suggest a higher MC density presence in more severe disease. Despite the small sample size (n=20/group, similar to those cohorts used in other publications^{16,24}), these significant correlations suggest our findings are worthy of validation in additional cohorts to determine a direct association of MC density and mortality. Interestingly, increases in MC number were not only associated with IPF as we also showed that MCs were increased in chronic HP (but not NSIP), and fibroblastic foci are a hallmark of the usual interstitial pneumonia pattern of fibrosis that is characteristic of IPF and occasionally found in chronic HP. Moreover, an association between MCs and IPF was strengthened by our findings in a separate cohort where we observed increased MC protease signature (CPA3, TPSAB1 and TPSB2) as well as SCF gene expression, one of the key factors involved in MC survival, proliferation and activation.^{41,42}

Enhanced fibroblast number, activation and myofibroblast differentiation are detected in IPF lung. These cells are capable of laying down ECM and causing lung stiffening.³⁸ Our observation that MC density was highest in the region immediately surrounding the fibroblast foci, specifically in areas of established fibrosis, corroborates the hypothesis that the MC–fibroblast interaction exists in IPF. Furthermore, we confirmed previous evidence that MC–fibroblast crosstalk is pro-fibrotic, by demonstrating that MCs induced fibroblast proliferation and increased α SMA fibre formation.^{17,21,23} An additional pro-fibrotic role for MCs has recently been suggested by Shimbori and colleagues, who demonstrated that the fibrotic lung ECM regulates MC function and that degranulating MCs induce TGF- β 1 activation.²⁰ Our observation that the chymase+ MCs and the dual positive MCTCs were significantly increased in IPF compared with non-fibrotic controls implies that the MC pro-fibrotic activity may be related to these subtypes, although we saw a trend across all MC subtypes. This hypothesis is consistent with Andersson and colleagues who proposed that MC subtypes are switched towards the double positive MC_{TC} phenotype in IPF²⁴ and with Shimbori and colleagues who recently observed an increase in MC_{TC}s in IPF lung,²⁰ although it should be noted that we observed fewer MC_{TC}s compared with Andersson and colleagues, which could be due to the analysis techniques used. Collectively, our data provide evidence that MCs are increased in IPF lungs, possibly due to increased levels of SCF in the lung, and thus may play a pro-fibrotic role in the pathogenesis of the disease.

Since MCs express the receptor tyrosine kinase ckit (the receptor for SCF), we investigated whether nintedanib, a broad-spectrum tyrosine kinase inhibitor, impacted MC survival or function and also compared its mechanism of action on MCs with pirfenidone. Interestingly, nintedanib but not pirfenidone reduced SCF-mediated MC survival, at concentrations below the reported cmax for nintedanib (ie, 30nM; the maximum plasma concentration achieved at steady state with 150mg twice daily dosing is 70nM),⁴³ indicating these effects are achievable with physiologically relevant concentrations of nintedanib. Decreased MC survival was also observed at lower concentrations (online supplementary figure S5). Of note, the CBMCs used in these assays did not proliferate in co-culture with fibroblasts, which is in contrast to the effect observed with human lung MCs in co-culture,^{17,44} and may reflect differences between CBMCs and human lung MCs. Importantly, we demonstrated that the effects of nintedanib were mediated via the ckit receptor and provided evidence that nintedanib attenuated SCF-mediated ckit phosphorylation, which reduced subsequent MC proliferation and CCL2 release from these cells. Since the adhesion molecule cell adhesion molecule 1 (CADM1) has been shown to interact with ckit and promote MC survival,^{44,45} it is plausible that nintedanib's effect on ckit could disrupt this interaction. One potential limitation of this work is that due to the impact of nintedanib on MC survival, we have not demonstrated a direct effect of nintedanib on MC-mediated fibroblast proliferation or activation. Nevertheless, to our knowledge, this is the first data demonstrating that nintedanib can inhibit ckit activation and reduce human MC survival and function.

Since access to lung tissue in patients before and after nintedanib treatment is not currently feasible, we availed of a rat bleomycin model to study the effects of this drug on MC survival or recruitment in vivo. Notably, nintedanib prevented the bleomycin-induced increase in lung MCs, confirming its activity on MC recruitment, although whether this is due to a direct effect of nintedanib on MC ckit or indirectly via effects on other cells is unclear. However, the effect of nintedanib on fibrosis was variable; we noted a significant reduction in high density tissue (HDFm) by quantitative image analysis, however little impact was seen on whole lung hydroxyproline levels. The regional image analysis method is perhaps more sensitive to detect subtle altera-

tions in the parenchyma and less affected by the patchy nature of fibrosis or the contribution of airway collagen.³¹ The bleomycin model has limitations for modelling the development of fibrosis in human disease and a longer time point (ie, >2 weeks) may have been required to see greater anti-fibrotic effects with nintedanib, and determine whether nintedanib can deplete resident MCs, which are long lived.⁴⁶ There are conflicting data on the effect of MC depletion in rodent bleomycin models, with MCs appearing pro-fibrotic in some studies and protective in others.^{19–47–49} Bradding and Pejler suggest this may relate to the short duration of injury exhibited in the rodent models versus the more chronic injury observed in human IPF.⁵⁰ Nevertheless, our findings are largely consistent with studies showing nintedanib reduces fibrosis in rodent models,^{30,51} but here we importantly expand this drug's mechanism of action to impacting MC numbers in vivo. Future studies using cultured human lung tissue from healthy individuals or patients with IPF, such as precision cut lung slices, could examine the effects of nintedanib treatment on human lung MCs in a more physiologically relevant multicellular assay system. This would also enable us to determine if other disease-associated factors could compensate for the ablated SCF signalling and also inhibit other potential cellular sources of SCF.

In summary, we have presented novel data suggesting that nintedanib inhibits MC survival both in vitro and in vivo via ckit; however, the efficacy of nintedanib in IPF likely resides in the drug's ability to modulate multiple fibrotic pathways. For nintedanib, these positive effects include an impact on the receptors for VEGF, FGF and PDGF.³⁰ Furthermore, nintedanib can act on a number of other tyrosine kinases, including Src, Flt3, Lyn and Lck,⁵² suggesting that the impact on MC function could also be mediated via other tyrosine kinases as shown for Lyn⁵³ in addition to the novel effects shown here on ckit. Interestingly, Imatinib (Gleevec), an inhibitor of ckit, PDGFR and c-abl, was not efficacious in an IPF clinical study; however, the effects on MC density and function in this study are unknown.²⁵ Pirfenidone is known to have antioxidant effects as well as blockade of TGF- β 1 signalling and inhibitory effects on PDGF, but the precise receptor and anti-fibrotic mechanism of action is unknown.²⁹ The lack of effect of pirfenidone on MCs in our studies may differentiate these therapies in IPF. Future work should be directed to investigate how nintedanib modulates MC functions in patients with IPF to determine whether there is a patient population that may gain additional benefits from treatment with nintedanib. Understanding the anti-fibrotic mechanisms of action of nintedanib could also enable the discovery of better novel therapies that more specifically target pro-fibrotic mechanisms and minimise the side effects associated with this therapy.⁴³ Furthermore, it is plausible that nintedanib could be efficacious in other respiratory diseases where MC density is elevated, such as asthma and COPD,⁵⁴ and further investigation is required to determine if nintedanib could ameliorate day-to-day airway dysfunction or the development of fixed airflow obstruction.

In conclusion, our data suggest that the ability of nintedanib to impair MC survival and activation may be a novel and additional mechanism by which nintedanib exerts its anti-fibrotic effects in patients with IPF.

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Acknowledgements We thank Mahmuda Khutan and Jingya Wang for statistical advice, and Dominic Corkill for in vivo study design expertise. We thank Biocellvia for their image analysis services and Oracle Bio for their histological staining services. We thank the laboratory of gisli Jenkins (University of Nottingham) for the iPf fibroblasts and gerard criner for the Temple study samples. We also thank alison humbles and Donna Finch for their editorial input into the manuscript.

Contributors CO-s designed and performed the research, analysed the data and wrote the manuscript; eM, rD, eLM, IB, Dr, hP, ac, ac, sK and gg-g performed the research; eM provided critical input to histological assessments; hP and Dr provided critical input to study cohort design; MK conducted bioinformatic analyses; al co-ordinated histopathological assessments; IM, rM and Dc planned the project and conceived the experiments. all authors read and approved the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests At the time of this study, all authors apart from Dr, hP and sK were employees of Medimmune (part of the astraZeneca group). Dc is now an employee of galapagos. CO-s, IM, al, sK, gg-g and eLM are current AstraZeneca employees and have stock/stock options in astraZeneca, and CO-s and IM are developing drugs for iPf. Patient consent for publication not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. additional gene expression data are available on reasonable request.

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A utilidade de um rastreio regular para a deficiência de alfa-1 antitripsina em doentes com bronquiectasias

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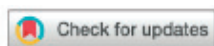
Received 12 October 2019

Revised 15 February 2020

Accepted 18 March 2020

Published Online First

17 April 2020



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Para citar: Carreto L, Morrison M, Donovan J *et al.* Thorax 2020;75:592–593.

RESUMO

A deficiência de alfa-1 antitripsina (DAAT) é uma causa de bronquiectasias. As diretrizes para as bronquiectasias da Sociedade Torácica Britânica não recomendam o rastreio regular de doentes para DAAT. Em contrapartida, as diretrizes para a DAAT recomendam o rastreio regular. Esta contradição resulta, em parte, da falta de dados de grandes estudos que efetuem rastreios abrangentes. Rastreámos 1600 doentes com bronquiectasias em dois centros no Reino Unido, entre 2012 e 2016. No total, apenas foram identificados oito indivíduos com DAAT, representando 0,5% da população total. Concluímos que o rastreio regular da DAAT em bronquiectasias no Reino Unido tem uma taxa de deteção reduzida. São necessários mais estudos em diferentes regiões geográficas, onde possa existir uma maior prevalência de DAAT.

Bronchiectasis is a heterogeneous airway disease characterised by chronic respiratory symptoms and permanent dilatation of bronchi. Guidelines from the European and British Thoracic Societies recommend systematic investigations for underlying causes, since there is specific treatment for some diseases that could have clinical and prognostic impact.^{1,2}

Alpha-1 antitrypsin deficiency (AATD) is a potential cause of bronchiectasis and augmentation therapy is licensed in several countries, particularly in cases of severe disease with airway obstruction.³ Prevalence of PiSZ and PiZZ phenotypes, the two most common phenotypes associated with lower serum alpha-1 antitrypsin (A1AT) levels and increased risk of lung disease, has been estimated to be 1:900 and 1:15.388, respectively, in the overall population in Scotland with a higher prevalence of 1:4440 reported in England.⁴

The clinical utility of AATD screening in bronchiectasis patients remains unclear. The British Thoracic Society guidelines currently recommend against screening for AATD-based primarily on the results of Pasteur *et al*⁵ who screened 150 patients with bronchiectasis and found a frequency of AATD which was not different to the general UK population. No patients with SZ or ZZ phenotype were identified in this study.⁵ A retrospective study of 202 patients with bronchiectasis from France (1991–1996) found a distribution of alpha-1 phenotypes that was not different to the distribution expected in the general population.⁶ In contrast, bronchiectasis has been reported frequently in patients with known AATD.⁷ For example Parr *et al* studied 74 patients with PiZZ genotype and found that 95% had bronchiectasis affecting a mean of 3.7

lobes. 27% had bronchiectasis affecting more than four lobes and daily sputum production.⁷ Based on data such as this, guidelines for AATD suggest screening all patients with bronchiectasis for AATD.⁸ This contradiction, where bronchiectasis guidelines recommend against screening while AATD guidelines recommend routine testing, results in part from the lack of any large prospective studies evaluating the results of routine prospective screening.

We, therefore, investigated if routine measurement of serum A1AT in the aetiological assessment of bronchiectasis was clinically useful in two large populations of UK adults.

New patients attending the Bronchiectasis Clinics at Ninewells Hospital and the Royal Brompton Hospital, London (RBH) for initial investigation of bronchiectasis aetiology were included in the study. All patients had documented bronchiectasis by high-resolution CT (HRCT) scans. Standardised testing for aetiologies of bronchiectasis was performed including A1AT testing, but also testing for allergic bronchopulmonary aspergillosis (ABPA), immunoglobulins, functional antibodies and serum electrophoresis. Serum A1AT level was measured according to the local laboratory standard procedures and in cases where the serum level was low, phenotyping was performed. At the Ninewells laboratory, the level for phenotyping was 1.0g/L and at RBH it was 1.3g/L.

Between January 2012 and December 2016, 675 people with bronchiectasis were investigated at Ninewells Hospital and 925 patients were investigated at RBH. Characteristics of patients at both centres have been previously reported and are predominantly elderly females (median 67 years, 60% female).

At the Scottish centre, we identified 17 patients (2.52%) with A1AT levels <1g/L who went on to have phenotyping performed. In those with an abnormal A1AT level, the mean was 0.79g/L (+/–0.18). Phenotypes were PiMZ in 13 patients (average 0.86g/L+/–0.09), PiSZ in three patients (average 0.7g/L+/–0.06) and PiZZ in one patient (0.20g/L. We, therefore, identified one patient with severe AATD disease (PiZZ) from 675 screened and three patients with moderate AATD disease (PiSZ). The minimum protective level of A1AT has been reported as 0.8g/L. On this basis we identified six individuals with deficient A1AT levels.

From the 925 patients screened at RBH 254 patients had phenotyping performed due to a level <1.3g/L of which 21 had levels <1g/L equating to the Ninewells cut-off. From phenotyping we identified seven patients with PiZZ with an average level of 0.23g/L (0.05), three patients with

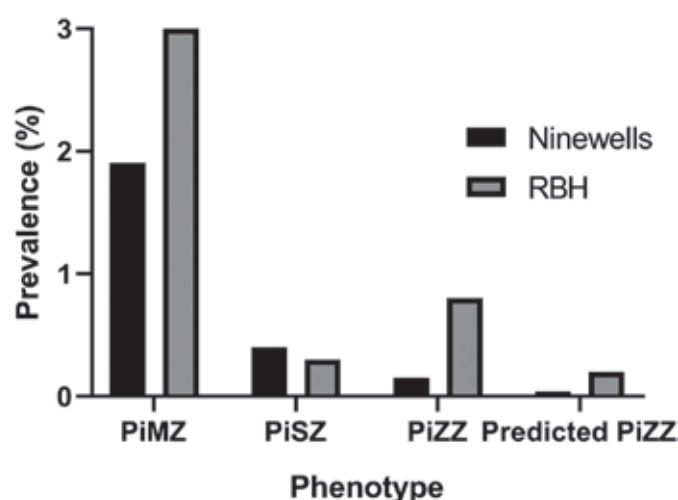


Figure 1 Frequency of different alpha-1 antitrypsin deficiency phenotypes in the two cohorts. Predicted values are the % of subjects expected to be identified in the general population based on reported population frequencies of PiZZ alpha-1 antitrypsin deficiency (unweighted prevalence estimates).^{3,4} RBH, Royal Brompton Hospital.

PiSZ or PiS where the second allele could not be identified with an average of 0.93 (0.23). Twenty-eight patients were identified with PiMZ with an average of 1.01g/L (0.16). Eight patients had A1AT levels below the protective threshold of 0.8g/L. Results are summarised in figure 1.

Augmentation therapy is recommended only to non-smoking patients with pulmonary emphysema and reduced or progressive decline on lung function.³ Non-smoking PiMZ individuals are not known to have increased risk of lung disease⁹ and PiSZ phenotype is not usually an indication for augmentation therapy, therefore, in 675 bronchiectasis patients, only one (0.15%) patients in Scotland and 7 (0.8%) in England had severe AATD that could possibly benefit from augmentation therapy. The slightly higher prevalence in England may reflect true differences as the reported prevalence is higher in England, or differences in the characteristics of patients referred to each centre.

In the UK, National Health System, A1AT serum assay and phenotyping costs were £2.45 and £35.50, respectively, which means that the total cost of screening in this project was £2257.25 to identify a single individual eligible for treatment in the Scottish site and £11283.25 to identify seven patients eligible for treatment in the English site. The higher costs at the English site reflect a higher number of patients included and the lower threshold for phenotyping of 1.3g/L.

Augmentation therapy have been shown to reduce, but not eliminate, emphysema progression³ and to reduce the frequency of hospital admissions for acute exacerbations of chronic obstructive pulmonary disease.¹⁰ However, to our knowledge, there have been no studies evaluating clinical benefits for bronchiec-

tasis patients with AATD. It is important to note that augmentation therapy, despite its clinical benefits in selected patients, is not available in some countries, including the UK.

Early diagnosis of AATD is important for much more than augmentation therapy, as these patients also benefit from smoking cessation programmes and genetic counselling. Awareness that patients have impaired protease-anti-protease balance may lead to closer monitoring and a lower threshold to treat chronic infection. However, our findings show that the prevalence of AATD in bronchiectasis patients is relatively low compared with other reported aetiologies which are routinely screened for such as ABPA, and that implementation of routine screening of these patients does not significantly impact on clinical management. Our results are derived from two UK centres and a predominantly Caucasian population. It is possible that a higher rate of detection of AATD would be found in other geographical regions in the UK, or in other countries. The study has limitations including that we screened two unselected bronchiectasis populations and did not collect detailed phenotypic data. We cannot, therefore, comment on whether more focused screening, for example, by limiting testing to those with airflow obstruction or CT detected emphysema, would have a great pickup rate. This will require further studies. A multicentre European cohort study that incorporates standardised testing for AATD is currently enrolling (NCT03791086) and will provide broader prevalence estimates as well as more detailed phenotypic data.

In summary, screening of an unselected UK bronchiectasis population for AATD identifies severe AATD in less than 1% of cases.

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Contributors Study design: JDC, TF, EF, RW and ML. Collected data: LC, MM, JD, SF, GLT, TF, ML and JDC. Performed analysis: LC, MM, ML and JDC. Wrote the manuscript: LC and JDC. Edited the manuscript and approval the final version: all authors.

Funding This study was funded by British Lung Foundation (BLF chair of respiratory research).

Competing interests ML declares personal fees from Grifols, Bayer, Polyphor and Astrazeneca. JDC declares research grants or personal fees from Glaxosmithkline, Boehringer-Ingelheim, Astrazeneca, Pfizer, Bayer, Grifols, Aradigm, Napp and Insmed outside the submitted work.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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Persistência da imunidade em crianças imunizadas com vacina pneumocócica conjugada 13-valente e impacto sobre a colonização nasofaríngea: um estudo transversal

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2019-213878>).

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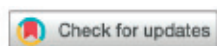
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Received 26 July 2019
Revised 16 April 2020
Accepted 17 April 2020
Published Online First
22 May 2020



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Para citar: Janapatla RP, Hsu MH, Chen C-L, et al. *Thorax* 2020;75:689–692.

RESUMO

Em 500 crianças com idade ≤10 anos após imunização com vacina pneumocócica conjugada 13-valente (VPC) em diferentes cronogramas, previu-se que imunoglobulina G (IgG) específica do serotipo 19A e 19F persistiria acima dos 0,35µg/mL durante ≥10 anos em todos os grupos, provavelmente devido à memória imunológica induzida pela VPC13 com o impulso natural de doenças residuais e colonização. Geralmente, a IgG de serotipo específico poderia persistir acima de 0,35µg/mL por mais tempo (≥5 anos) no grupo de recuperação do que nos grupos de imunização 2+1 e 3+1. 14,5% dos isolados de colonização pertencem aos serotipos VPC13. A análise estatística revelou que será necessário um nível sérico elevado de IgG (>10,96µg/mL) para eliminar o ponto de prevalência de colonização nasofaríngea do serotipo 19A.

INTRODUCTION

There is a scarcity of data on the long-term persistence of immunity after 13-valent pneumococcal conjugate vaccine (PCV13) immunisation and its impact on nasopharyngeal carriage. The national PCV13 catch-up programme implemented during 2013–2014 and the inclusion of PCV13 in the national immunisation programme in 2015 had successfully reduced the incidence of invasive pneumococcal disease (IPD) from 17.8/100 000 in 2012 to 5.5/100 000 in 2017 among children aged 0–5 years; however, information about the populationwide immunogenicity post-PCV13 vaccination remains unknown.¹ We conducted a cross-sectional study in 2016–2017 to assess the persistence of immunity after the administration of PCV13 in three different schedules introduced over the years in children in Taiwan and the impact of PCV13 immunisation on nasopharyngeal carriage.

METHODS

This cross-sectional study in 2016–2017 enrolled 500 children aged ≤10 years who were previously administered with PCV13 according to different schedules in 2009–2017. These children were divided into four groups on the basis of the immunisation schedule, including catch-up (1–2 doses of PCV13 (n=257), 2+1 (n=60), 3+1 (n=164), and those without vaccination (n=19) (see online supplementary figure S1 and table S1).

Immunoglobulin G (IgG) antibody titres specific for eight serotypes (3, 6A, 6B, 7F, 14, 19A, 19F and 23F) were determined by ELISA.² In a subset of 50 sera, opsonophagocytic activity (OPA) was determined for serotypes 1, 3, 5 and 19A by multiplex OPA at a WHO Reference Laboratory in Institute of Child Health, University College London, UK.³

Serotyping was performed by latex agglutination and confirmed by Quellung reaction (Statens Serum Institut, Copenhagen, Denmark). A multiplex polymerase chain reaction serotyping was

also performed as described previously.⁴ Linear regression analyses were performed to assess the persistence of anticapsular polysaccharide IgG after PCV13 vaccination; correlation between serum IgG (µg/mL) and time (years) after vaccination was evaluated using Pearson's correlation coefficient (r).³ A logistic regression model was used to analyse the association between nasopharyngeal carriage and IgG concentration for each serotype.³ Additional information is included in online supplementary materials and methods.

RESULTS

No significant differences were found in the population-wide geometric mean concentrations (GMCs) among the catch-up, 2+1 and 3+1 immunisation groups for the majority of serotypes examined in this study (see online supplementary table S2 and figure S2). GMCs for serotype 3 were low at approximately 0.30µg/mL in different groups. GMC for serotype 19A in the 3+1 group was higher but not significant (p>0.744) when compared with other groups.

Four to six years after the PCV13 booster dose, IgG levels remained significantly high (p<0.05) for serotype 19A and significantly low (p<0.05) for 7F in all the groups (see online supplementary table S3). Regression lines and equation predicted that IgG titres against 19A and 19F serotypes could persist above the IPD protective threshold for >10 years in all the study groups (figure 1), in contrast a higher proportion of serotype 3-specific IgG titres was persistently below the threshold. There was a gradual decrease in serotypes 6A-specific, 6B-specific, 7F-specific and 14-specific IgG over time in all groups (figure 1). Only 19A-specific IgG titres showed a positive correlation (r=0.117–0.216) with time after vaccination in all the three groups, and there were >89% of children with IgG levels above the IPD protective threshold in all groups (figure 1, online supplementary figure S3 and table S3).

The proportion of subjects reaching both the seroprotective thresholds (IgG ≥0.35µg/mL and OPA ≥8) for serotypes 1, 3, 5 and 19A were 30.4, 36.2, 67.4 and 92%, respectively (see online supplementary figure S4A). Overall, for serotype 3, a high percentage (53.2%; 25/47) of subjects could not reach the IgG level of ≥0.35µg/mL; however, among them, 31.9% (15/47) attained functional OPA titre of ≥8 and the geometric mean titre was 36.64 (see online supplementary figure S4B). Serotype 19A-specific functional OPA titres were found to be elevated and stable for 2–5 years in 66% of the subjects (see online supplementary figure S4C).

Among the 500 children, 135 (27.0%) were positive for pneumococcal carriage and overall 20 (4%) carried PCV13 serotypes. The predominant vaccine serotype was 19A and the most prevalent non-vaccine serotypes were 23A, 15B/C and 34 (figure 2A,B). None of the children were colonised with PCV13 serotypes 1, 3, 4, 5, 7F, 9V and 18C.

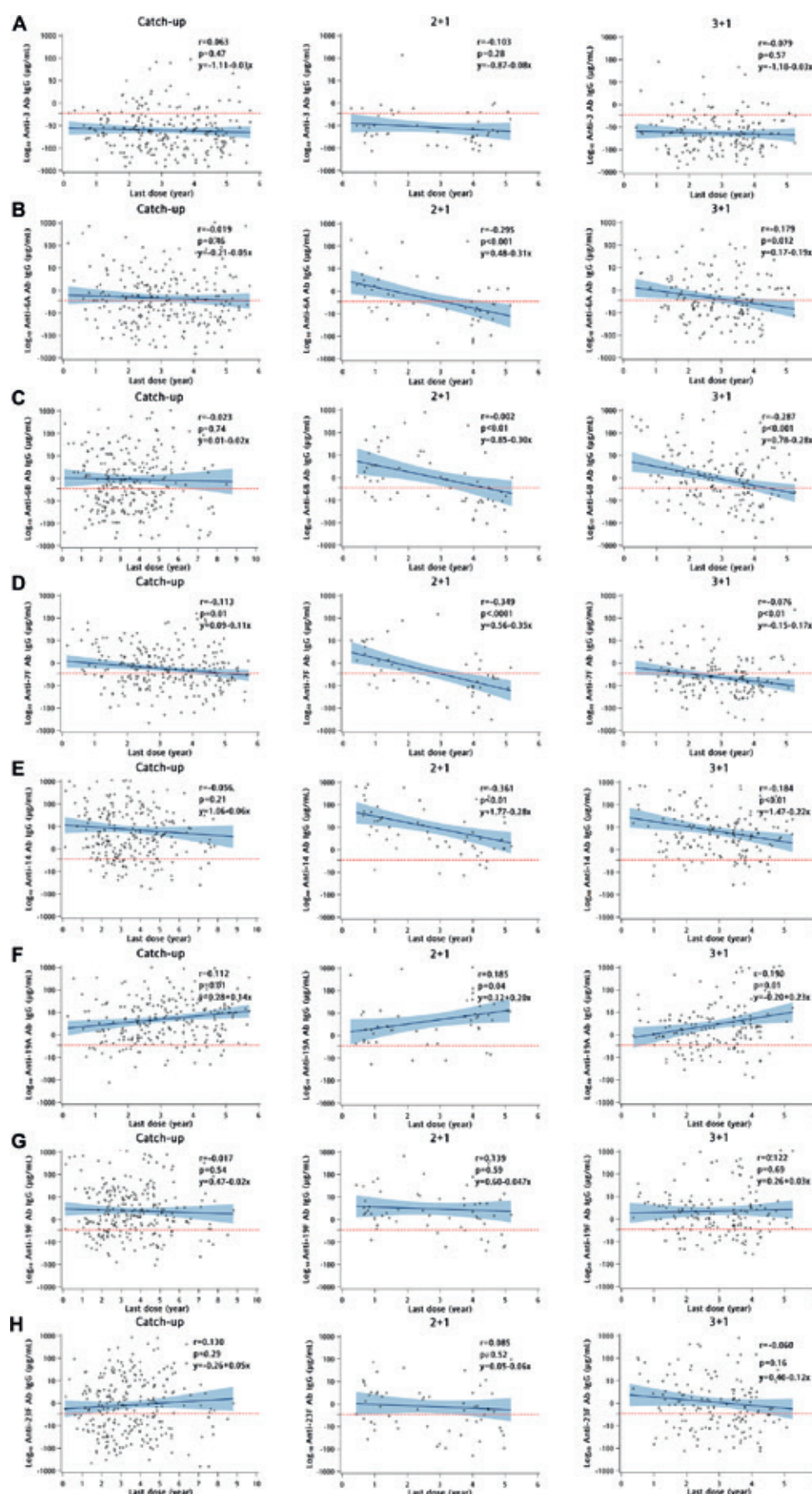


Figure 1 Scatter plots showing linear regression lines and correlation coefficients between log IgG antibody titres with time (years) after PCV13 vaccination in children with catch-up (1–2 doses), 2+1 and 3+1 schedules. The individual titres are indicated by dots. Correlation coefficients were determined with the Pearson correlation test. *r*, Pearson correlation Coefficient. *P* values <0.05 were regarded as statistically significant. Solid blue line is the regression line and the shaded blue region represents 95% CI of the regression line. Panels A–H refer to serotypes 3, 6A, 6B, 7F, 14, 19A, 19F and 23F, respectively. Time since last PCV13 dose ranged from 1 month to 9 years. Serotype 19A epidemic peaked in the years 2011 and 2012 in Taiwan; this time period corresponds to 4–6 years post last PCV13 dose. IgG, immunoglobulin G; PCV13, 13-valent pneumococcal conjugate vaccine.

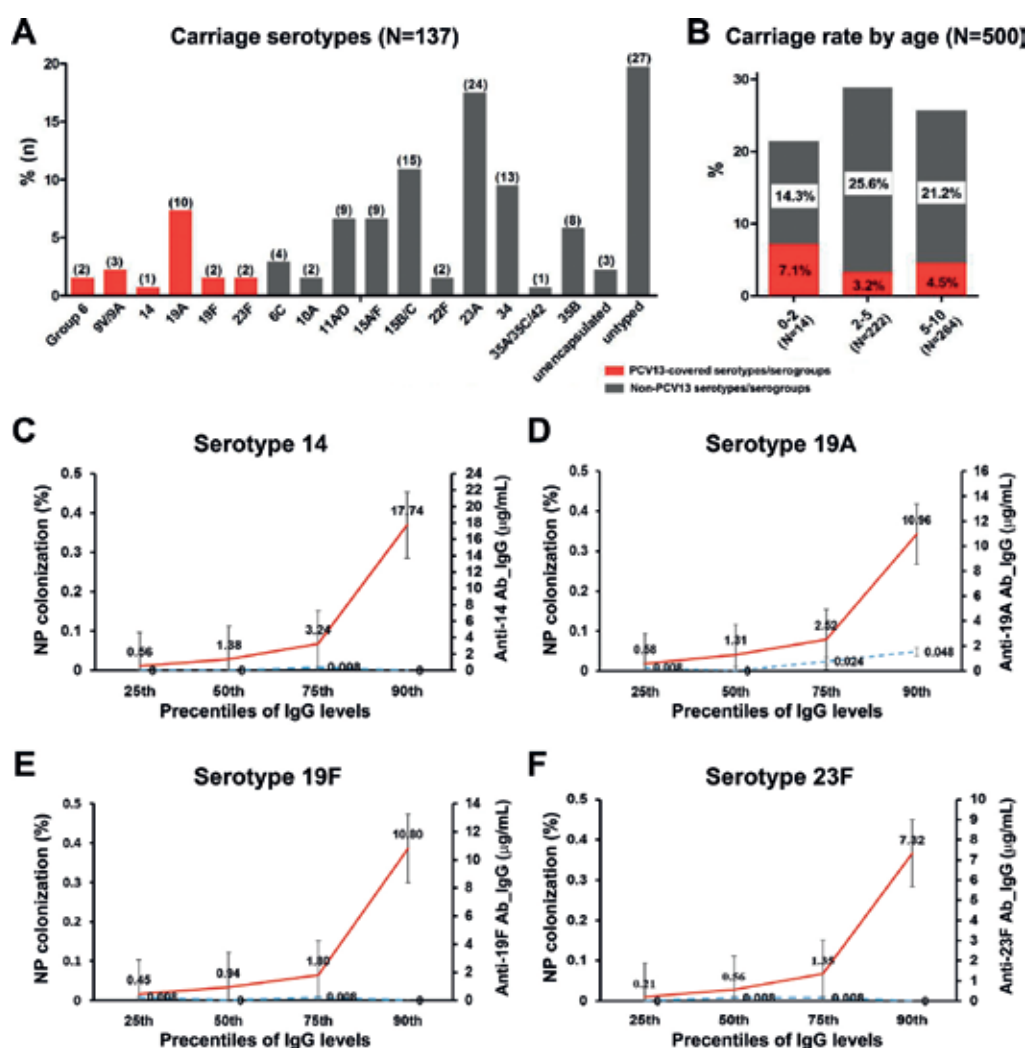


Figure 2 Nasopharyngeal carriage of *Streptococcus pneumoniae* in children vaccinated with PCV13 in 2016–2017. Panel A displays serotype distribution of *S. pneumoniae* isolates. Number of isolates per serotype is in parentheses. PCV13 (red bars) and non-PCV13 serotypes (black bars). Panel B displays carriage rate of *S. pneumoniae* isolates of PCV13 serotypes (red bars) and non-PCV13 serotypes (black bars) by age group. The carriage rate was computed by dividing the number of positive samples by the total number of samples collected. Panels C–F display predicted point-prevalence carriage rates for serotypes 14, 19A, 19F and 23F corresponding to IgG concentration after PCV13 vaccination in 500 children. For each serotype, subjects were tested for IgG antibody levels and nasopharyngeal carriage of *S. pneumoniae*. The predicted changes in point-prevalence nasopharyngeal carriage rate corresponding to the antibody concentration threshold of ≥ 0.35 $\mu\text{g/mL}$ and to selected percentiles of IgG concentration were calculated for the total population. Red line represents the IgG antibody levels in the secondary axis, and the blue dotted line represents the percent of nasopharyngeal carriage in the primary axis. IgG, immunoglobulin G; PCV13, 13-valent pneumococcal conjugate vaccine.

The carriage rates of PCV13 serotypes were low and there was no evidence of a statistically significant relationship between IgG concentrations and carriage rates, except for serotype 19A (figure 2C–F). Despite the fact that no difference was found for serotypes 14, 19F and 23F, the point-prevalence nasopharyngeal carriage rates were 0 at the 90th percentile of IgG titres for the three serotypes. The carriage rate for 19A slightly increased with an increase in serum IgG titres. The odds of carriage were similar for all serotypes, whereas the odds were statistically significant for 19A only ($p=0.0061$, online supplementary table S4).

Comparison of pneumococcal carriage rates with IgG percentiles revealed that a serum IgG level >10.96 $\mu\text{g/mL}$ is associated with a low point-prevalence nasopharyngeal carriage rate of serotype 19A (figure 2D).

DISCUSSION

Long-term immunogenicity studies on CRM197-based PCVs have been largely based on PCV7, indicating that serum IgG levels against vaccine serotypes remained ≥ 0.35 $\mu\text{g/mL}$ in the majority of children for at least 4 years after the booster.^{5 6} In this study, trend lines predicted that IgG titres against the predominant nasopharyngeal isolates in 2010–2014 (19A and 19F) in this region could persist above 0.35 $\mu\text{g/mL}$ for >10 years in both the 2+1 and 3+1 immunisation groups, but the antibody concentrations and the

persistence for the rare serotype 7F were lower (<3 years) in both groups.

Interestingly, trend lines revealed that IgG levels could persist for ≥ 10 years for the prevalent PCV13 serotypes in the catch-up group. Since the age (2.97 ± 0.12 years) at the administration of the last dose in the catch-up group was >20 months, compared with 1.22 ± 0.15 years in the 2+1 group and 1.08 ± 0.03 years in the 3+1 group, administration of PCV13 to older children could induce a stronger immune response. This observation was consistent with a previous case–control study that found that the incidence of vaccine-type (84%, 19A) severe pneumococcal pneumonia was significantly less in children with catch-up schedules (7.1%) compared with that in children with the 2+1/3+1 schedule (24.1%) and in age-inappropriate, under-immunised children (28.6%).⁷ Some clinical trials of PCVs also observed a robust immune response to one dose of PCV13 in previously immunised children aged 2–5 years.^{5 8}

In a subset of 50 subjects from the three groups, serotype 3-specific IgG titres that reached the protective level (≥ 0.35 $\mu\text{g/mL}$) were found only in 46% of the children, whereas the OPA titres that achieved the threshold ($\geq 1:8$) were found in 68.1% of the children, suggesting that some sera with lower IgG titres were OPA-positive. Despite the low levels of serotype 3-specific IgG titres in the study population, none of the children were colonised with serotype 3 isolates. Together, these observations support the notion that func-

tional OPA may be a better predictor of protection than serum IgG for some serotypes such as serotype 3.

Among PCV13 serotypes, 19A carriage rate in our earlier study (5.0%, 2014–2015) was not different from this study (7.4%, 2016–2017); the persistent carriage might partially explain the 19A residual infections occurring in Taiwan. After the introduction of PCV13 initially as a catch-up schedule in 2013–2014, the incidence of IPDs caused by 19A in children aged 0–5 years has decreased significantly.¹ In Australia, after introduction of the 3+0 schedule, the incidence of 19A IPDs decreased significantly, but 19A persisted as the predominant PCV13 serotype causing breakthrough IPD in the second year of life.⁹ Our data also demonstrated that a single '19A-like' epidemic serotype did not emerge from the non-vaccine serotypes in the post-PCV13 era, but isolates belonging to serogroup 15 and serotypes 23A, 11A, 35B and 34 have emerged with high prevalence. However, these non-vaccine serotypes tended to exhibit less invasive potential, thereby contributing to the overall decline of IPD.¹⁶

Both colonisation and residual diseases caused by serotypes 19A and 19F contributed to the natural boosting of serotypespecific antibodies that subsequently could persist for ≥ 10 years.^{1,6,8} Given the current carriage rate of 2.0% for serotype 19A, very high concentration of serum IgG ($>10.96\mu\text{g/mL}$) will be required to eliminate the carriage. Alternatively, we could also hypothesise that after the last dose of PCV13 a new acquisition and colonisation of vaccine serotype is still possible in some children despite the presence of high-level serotypespecific IgG. These conclusions reflect this cross-sectional study conducted in the PCV13 era without the baseline carriage rates in the same population for comparison. Previous studies also showed that natural exposure to circulating serotypes increases antibody titres, but higher antibody titres are required to prevent colonisation and infections by frequently carried serotypes, including 19F and 19A.^{10,11} Therefore, a common correlate of protection against colonisation for all serotypes could not be established and the predicted correlates varied among studies in children and adults.^{3,12} Further studies are necessary to discover better correlates of protection

derived from memory B cells or nasal wash IgG titres.¹¹ These new models for *Streptococcus pneumoniae* acquisition and carriage could give us better prediction results.

Acknowledgements The authors thank the children and their families for participating in this research with prior consent. The authors thank for the statistical assistance and acknowledge the support from the Maintenance Project of the Center for Big Data Analytics and Statistics at Chang Gung Memorial Hospital for statistical consultation and data analysis.

Contributors C-HC conceived and designed the study. M-HH, S-HW and M-JY carried out the experiments. RPJ, M-HH, C-LC, S-HW, M-JY, L-HS, T-YL and C-HC performed the data analysis and figure/table preparation. RPJ and C-HC reviewed the literature, interpreted data and wrote the manuscript.

Funding This work was supported by Chang Gung Memorial Hospital (CMRPG3H0041, CMRPG3G1971, CMRPG3F1143 and CMRPG3F0083) and Ministry of Science and Technology (105-3011-F-182A-001), Taiwan.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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O isolamento social e a solidão como fatores de risco para admissões hospitalares por doenças respiratórias entre idosos

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2019-214445>).

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Received 12 December 2019

Revised 19 February 2020

Accepted 16 March 2020

Published Online First

21 April 2020



► <http://dx.doi.org/10.1136/thoraxjnl-2020-214873>



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RESUMO

As crescentes admissões hospitalares devido a doenças respiratórias (DR) representam um grande desafio para os hospitais. Este estudo explorou fatores de risco social modificáveis entre 4478 idosos do *English Longitudinal Study of Ageing*. Os dados foram ligados a registros hospitalares administrativos e dados de registro de mortalidade (seguimento de 9,6 anos) e foram analisados através de uma análise de sobrevivência que contabilizou os riscos concomitantes. Ao contrário do contacto social ou da solidão, viver sozinho e o afastamento social foram associados a um risco acrescido de admissão de DR, independentemente de fatores sociodemográficos, de saúde e de comportamento. O apoio a adultos socialmente afastados que vivam sozinhos e que estejam em risco de admissão por DR deve ser explorado.

INTRODUCTION

Hospital admissions due to respiratory disease (RD) have major health and economic costs,¹ are a central component of winter bed crises and emergency department congestion, and disproportionately affect more vulnerable parts of society such as older adults.² RD admissions have risen at three times the rate of all other reasons for hospital admission in recent years.² So, more research into modifiable risk factors for RD hospital admissions is clearly warranted.

To date, little attention has been paid to social factors such as social isolation and loneliness, despite a strong rationale for their influence. Both social isolation and loneliness have been linked with an increased incidence of morbidity and mortality³ and are associated with decreased medication adherence and health-seeking behaviours, and increased hospital admissions for a wide range of conditions including mental illness and heart failure.^{4,5} Both are also linked with biological responses related to poorer outcomes, for example, increased systemic inflammation.⁶

Preliminary studies have suggested that, for people with chronic obstructive pulmonary disease (COPD), social isolation may increase risk of winter hospital admission with RD,⁷ while loneliness may increase emergency department presentation.⁸ In addition, social activities such as group singing and dance are increasingly utilised in COPD management,⁹ with suggestions that they may reduce health service utilisation and hospital admissions.¹⁰ However, this research area is under-developed and there is no evidence from longitudinal representative data.

METHODS

This study assessed the relationship between loneliness, three different aspects of social isolation and RD hospital admissions in a large cohort of older adults in the English Longitudinal Study of Ageing (ELSA): a nationally representative biennial panel study linked to admitted patient care (APC) data from NHS Hospital Episode Statistics. In order

to consider the competing risk of death over the follow-up period, ELSA was linked with mortality data obtained from the UK National Health Service mortality registry. Using wave 4 data (2008/2009), 7270 of the 8780 participants provided consent to data linkage (87%), 90% of these provided spirometric data and 68% of these provided full data leaving a sample of 4478 (online supplementary figure S1). The APC data were available until January 2018, providing a maximum follow-up of 9.6 years.

RD admissions were defined as admittance to hospital with a primary diagnosis of RD. Social isolation was measured as living alone or not (domestic isolation), frequency of social contact with children, relatives and friends (social contact), and frequency of engagement with community groups, volunteering or cultural activities (social engagement). Loneliness was measured using the three-item UCLA loneliness scale. Confounders included socio-demographic factors (gender, age, ethnicity, an index of socioeconomic status comprised of education, social class and wealth, and an index of indoor and outdoor respiratory-related living environment deprivation), health-related factors (pre-existing diagnosed and undiagnosed COPD assessed spirometrically, comorbidities and depression) and behavioural confounders (smoking, heavy drinking, diet and physical activity). Cox causespecific hazard (CSH) models were used to model the time from the baseline interview until the first RD admission within the follow-up, accounting for death as competing risks events. Main analyses were carried out in Stata V.15. Please see the supplement for detailed explanation of the variables and method.

RESULTS

Demographics are shown in online supplementary table S1. 11% of participants had a RD admission within the follow-up period (online supplementary figure S2). Table 1 presents the results from the CSH models fitted progressively. Living alone was associated with a greater hazard of RD admissions even after adjusting for potential confounders. In the fully adjusted model (Model IV), people living alone had a 32% higher hazard compared with those who lived with others (HR=1.32, 95% CI 1.06 to 1.64). Social disengagement was also a predictor of RD admissions. One SD increase in social disengagement was associated with a 24% increase in the hazard of RD admissions (HR=1.24, 95% CI 1.11 to 1.38). However, neither low social contact nor loneliness was associated with RD admissions. The estimated cumulative hazards by domestic isolation and social disengagement are presented in figure 1.

Sensitivity analysis found very similar results when using multiple imputation (online supplementary table S2). Treating deaths from RD without a hospital admission (n=15) as RD admissions did not materially affect results (online supplementary table S3), nor did excluding people who had RD admissions in the previous 5 years (online supplementary table S4), or isolating the sample to individuals with

Para citar: Bu F, Philip K, Fancourt D, Thorax 2020;75:597–599

Table 1 Estimated HRs, p values and 95% CI from Cox models (n=4478)

Model I	Model II	Model III	Model IV
Living alone			
1.83	1.41	1.37	1.32
p=0.000	p=0.002	p=0.004	p=0.012
(1.49–2.24)	(1.14–1.75)	(1.10–1.69)	(1.06–1.64)
Low social contact			
0.98	0.96	0.96	0.96
p=0.720	p=0.307	p=0.349	p=0.328
(0.90–1.07)	(0.88–1.04)	(0.88–1.05)	(0.88–1.04)
Social disengagement			
1.56	1.42	1.33	1.24
p=0.000	p=0.000	p=0.000	p=0.000
(1.42–1.71)	(1.27–1.58)	(1.20–1.48)	(1.11–1.38)
Loneliness			
1.05	1.08	0.96	0.95
p=0.271	p=0.091	p=0.362	p=0.317
(0.96–1.14)	(0.99–1.18)	(0.87–1.05)	(0.86–1.05)

Model I was unadjusted. Model II controlled for socio-demographic confounders.

Model III additionally controlled for health-related confounders. Model IV additionally controlled for behavioural confounders.

acute RD admissions (online supplementary table S5). There was no evidence that findings were moderated by gender (online supplementary table S6) or pre-existing RD conditions (online supplementary table S7).

DISCUSSION

Overall, our results are broadly supportive of earlier research suggesting that aspects of social isolation, but not subjective loneliness, are associated with an increased risk of hospital admission.⁵ Potential mechanisms for the association between social isolation and RD admissions include a higher risk of being physically inactive and smoking among people who are socially isolated, less social pressure to seek medical attention early in the development of a RD and biological factors including isolation-related inflammation. Further, living alone is associated with poor health, disability and the risk of falls; hence, clinicians may admit patients due to increased discharge risks.

Our findings that social contact is not protectively associated could be because social contact carries increased risks of contagious respiratory conditions, more so than living with somebody (where there is a restricted germ pool) or social engagement (which might not involve close person-to-person contact in the same way

as seeing family or friends socially). This hypothesis, however, remains to be explored further.

The main strengths of this study include the use of a large-scale representative survey linked to administrative records with an almost 10-year follow-up and the consideration of a comprehensive range of identified confounding factors. However, as an observational study, causality cannot be assumed. Measurement error or unidentified confounders may affect results.

In conclusion, older adults living alone with existing lung conditions may benefit from additional targeted community support to try and reduce the risk of hospital admissions. The roll out of social prescribing schemes may present opportunities for referring these individuals to social engagement

Twitter Keir Philip @keirphilip

Acknowledgements The English Longitudinal Study of Ageing was developed by a team of researchers based at the University College London, NatCen Social Research, the Institute for Fiscal Studies and the University of Manchester. The data were collected by NatCen Social Research.

Contributors DF conceived the idea for this study. DF, FB and KP conducted the data analyses. The initial draft of the manuscript was produced by FB. DF, FB and KP were involved in interpreting the results and writing the manuscript. All authors read and approved the final manuscript.

Funding This research was supported through a grant from the Leverhulme Trust (PLP-2018-007). KP was supported by the Imperial College Clinician Investigator Scholarship. DF was supported by the Wellcome Trust [205407/Z/16/Z]. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript. The funding for English Longitudinal Study of Ageing is provided by the National Institute on Aging [R01AG017644] and a consortium of UK government departments coordinated by the Economic and Social Research Council.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Ethics approval for ELSA was granted by the National Research Ethics Service.

Provenance and peer review Not commissioned; externally peer reviewed.

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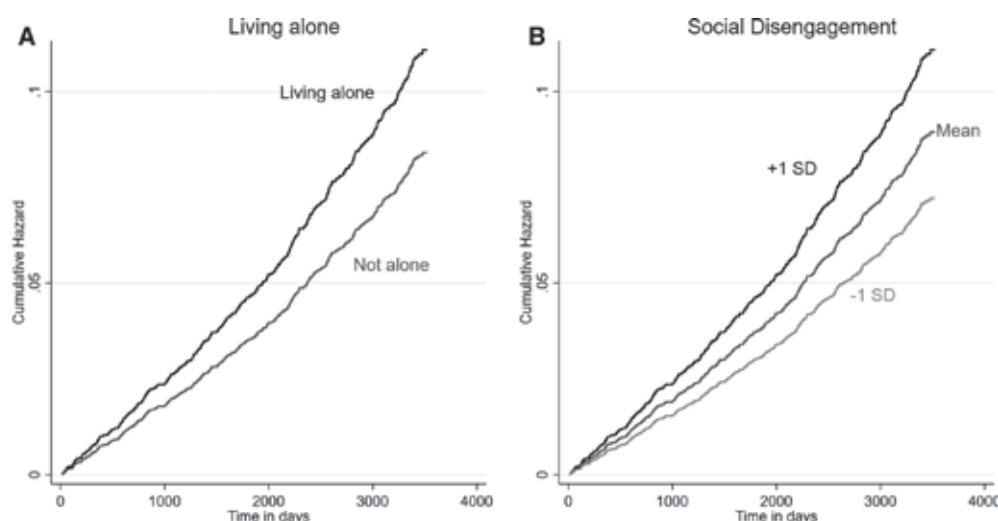


Figure 1 Estimated cumulative hazards by living alone and social disengagement.



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Received 18 march 2020

Accepted 29 april 2020

Published online First

15 may 2020



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Para citar: O'Carroll O, Sharma K, Fabre A, et al. Thorax 2020;75:706–707.

Lesão pulmonar associada ao vaping

Orla O'Carroll,^{1,2} Keshav Sharma,³ Aurelie Fabre,⁴ David J Murphy,⁵ Michael P Keane,^{1,2} Cormac McCarthy^{1,2}

Um homem de 18 anos apresentou-se no serviço de urgência de um hospital comunitário com tosse, febre, suores noturnos e perda de peso significativa. Recentemente, completou um curso de antibióticos para uma infecção do trato respiratório inferior. O hemograma completo revelou uma contagem normal total de leucócitos com contagem de eosinófilos de $0,85 \times 10^9/L$. A proteína C-reativa (PCR) foi normal, mas a taxa de sedimentação de eritrócitos (TSE) foi de 100mm/hora. A radiografia torácica demonstrou uma opacificação peri-hilar reticulonodular bilateral com preservação periférica (figura 1A). A imunoglobulina E estava ligeiramente elevada a 175UI/ml. Os restantes níveis de imunoglobulina, painéis virais e de autoanticorpos revelaram-se normais. A TC torácica de alta resolução revelou uma opacificação difusa centrilobular e peribronquial em vidro fosco em ambos os pulmões com preservação subpleural (figura 1B/C).

Na sequência da consulta, o doente revelou um histórico de vaping prolongado nos 6 meses anteriores, incluindo produtos com nicotina e tetrahidrocanabinol. Foi encaminhado para uma clínica especializada em doenças pulmonares intersticiais, onde os testes de função pulmonar realizados demonstraram espirometria normal, mas uma reduzida capacidade de difusão pulmonar para monóxido de carbono (DLCO) prevista de 60,3%. Realizou-se uma broncoscopia 4 semanas após a sua apresentação inicial, realizando-se uma nova radiografia torácica imediatamente antes do procedimento, demonstrando uma resolução acentuada em anomalias parenquimatosas (figura 2A).

Devido à melhoria das alterações radiológicas, não foram realizadas biópsias transbrônquicas, mas a lavagem broncoalveolar (LBA) revelou um diferencial celular de 66% de macrófagos, 27% de linfócitos, 4% de neutrófilos e 3% de eosinófilos (figura 2B). Aproximadamente 25% dos macrófagos alveolares eram espumosos e carregados de lípidos, comprovado por gotas de lípidos neutros evidentes no corante Oil-Red-O (figura 2C). Embora as aparências citológicas variassem ligeiramente dos relatórios recentes de apresentação aguda, considerou-se que a resolução na radiografia torácica e a presença de uma proporção significativa de macrófagos carregados de lípidos representavam uma lesão pulmonar em recuperação associada a vaping prolongado.

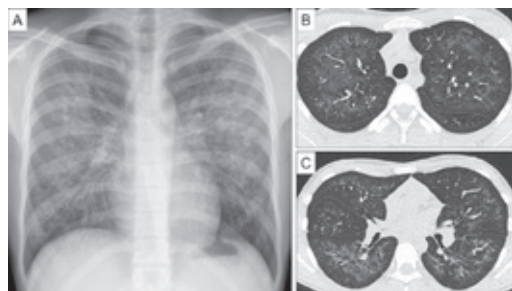


Figure 1 (A) Chest radiograph demonstrating extensive bilateral perihilar reticulonodular opacification with peripheral sparing. (B,C) Axial chest CT images demonstrate extensive bilateral centrilobular and peribronchial ground glass opacification with subpleural sparing, slightly more confluent in the lower zones.

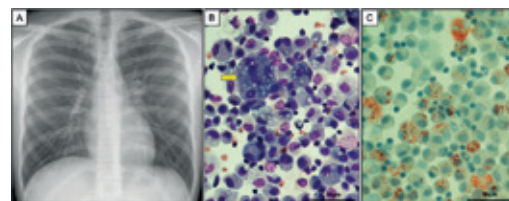


Figure 2 (A) Chest radiograph demonstrating complete interval resolution of the perihilar reticulonodular opacities. (B) Bronchoalveolar lavage (BAL) cytology stained with MGG $\times 400$ magnification demonstrating foamy macrophages, some multinucleated (yellow arrow). (C) Alveolar macrophages stained in red with ORO $\times 400$ magnification demonstrating presence of excess neutral lipid in alveolar macrophages. MGG, May Grunwald Giemsa stain; ORO, Oil-Red-O stain.

Após a cessação de todos os produtos de vaping, o doente melhorou e a DLCO melhorou significativamente 8 semanas após a apresentação inicial. A presença de macrófagos carregados de lípidos nas vias aéreas pode indicar a aspiração de material lipóide exógeno ou a presença de síndrome de proteinose alveolar pulmonar. No entanto, em casos de uso intensivo de cigarros eletrônicos, este pode ser um marcador útil da síndrome recentemente descrita: lesões pulmonares associadas ao uso de cigarro eletrônico e produtos de vaping (EVALI do inglês: *electronic cigarette and vaping associated lung injury*).¹ Embora os mecanismos fisiopatológicos não sejam claros, a presença de macrófagos carregados de lípidos tem sido reportada em muitos casos de EVALI.

Do mesmo modo, os casos demonstraram eosinofilia do sangue periférico (variando entre níveis normais e $2,9 \times 10^9/L$), TSE elevada (variando entre 60 e 128mm/hora) e níveis elevados de macrófagos carregados de lípidos na avaliação de LBA (variando entre 25% e 75%).¹ O acetato de Vitamina E é o éster sintético de tocoferol e o acetato é amplamente utilizado como agente espessante em produtos de vaping. Sugere-se que, quando inalado, o acetato de vitamina E pode interferir com a capacidade do surfactante pulmonar de manter a tensão superficial nos alvéolos e, quando aquecido, poderá formar ceteno, um conhecido irritante pulmonar.² Estudos recentes com modelos animais demonstraram níveis elevados de macrófagos carregados de lípidos de LBA em mancha de Oil-Red-O em ratos expostos a aerossóis gerados a partir de acetato de vitamina E.³ Este caso realça a utilidade da LBA e de Oil-Red-O na avaliação de EVALI e durante a resolução dos achados imagiológicos.

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Contributors all authors contributed to the conception, data collection and writing of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests none declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon request.

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Infeção assintomática por SARS-CoV-2: a ponta ou o iceberg?

Alexander J Keeley,^{1,2,3} Cariad M Evans,^{2,3} Thushan I de Silva^{1,2}

Os navios de cruzeiro, com o seu característico ambiente fechado, proporcionaram conhecimentos valiosos sobre a dinâmica da transmissão viral durante a pandemia da COVID-19. No navio de cruzeiro Diamond Princess, em Yokohama, Japão, aproximadamente 21% dos que se encontravam a bordo testaram positivo para o coronavírus 2 (SARS-CoV-2), com 51,7% destas pessoas a apresentar infeções assintomáticas na altura dos testes.¹ Na edição deste mês da Thorax, Ing *et al* descrevem um surto num navio de cruzeiro que parte da Argentina para a península Antártica com 223 passageiros, cuja temperatura e sintomas foram verificados antes do embarque em meados de março de 2020. Ao 8º dia, o primeiro passageiro desenvolveu sintomas.

Apesar da imposição imediata do isolamento na cabine a para todos os passageiros e da utilização obrigatória de equipamento de proteção pessoal pela tripulação, 128 (59,0%) dos que se encontravam a bordo testaram positivo para SARS-CoV-2 ao dia 20, quando todos foram submetidos a um teste baseado em RT-PCR. Dos que testaram positivo, apenas 24 (18,8%) desenvolveram sintomas e 104 (81,2%) permaneceram assintomáticos até ao 28º dia, quando desembarcou a primeira coorte de passageiros. É necessária alguma cautela na interpretação deste número, uma vez que o período de seguimento não é suficientemente longo para se ter a certeza de que todos os indivíduos permaneceram verdadeiramente assintomáticos.

No entanto, é impressionante que, apesar das tentativas rigorosas para limitar a propagação, tal transmissão generalizada tenha ocorrido a bordo. O ambiente fechado pode ser o principal condutor da elevada taxa de transmissão. Contudo, a possibilidade de casos assintomáticos terem contribuído significativamente para a propagação também deve ser considerada. A infeção assintomática é frequentemente entendida como a deteção do SARS-CoV-2 por RT-PCR na ausência de uma doença clínica compatível com a COVID-19. Na prática, as infeções assintomáticas reportadas abrangem uma mistura heterogênea de infeção paucissintomática (onde os sintomas estão presentes mas são leves ou não específicos), infeção préssintomática (onde a RT-PCR é positiva e os sintomas surgem pouco tempo depois), infeção não detetada (onde a RT-PCR é positiva numa pessoa que reporta retrospectivamente os sintomas) e infeção assintomática verdadeira (as que são monitorizadas ativamente durante 14 dias para o desenvolvimento dos sintomas). Independentemente da forma como estes casos são categorizados, qualquer caso em que haja uma infeção sem reconhecimento e, portanto, sem mudança de comportamento, existe o risco de subsequente transmissão.

Compreender a natureza e o papel da infeção assintomática por SARS-CoV-2 é fundamental para informar as estratégias de saúde pública no combate da COVID-19. São necessárias três etapas fundamentais: deve ser caracterizada a proporção de infeção assintomática por SARS-CoV-2, deve ser estabelecido o papel da infeção assintomática na transmissão subsequente em diferentes contextos e devem ser avaliadas as intervenções para o reconhecimento

e limitação da propagação de casos assintomáticos. Torna-se cada vez mais claro que o contexto da investigação é, provavelmente, responsável pelas estimativas abrangentes da prevalência da infeção assintomática e das proporções comunicadas até à data. Uma revisão sistemática, atualmente em pré-impressão, identificou cinco estudos com um quadro de amostragem claramente definido e um seguimento adequado para distinguir a infeção assintomática verdadeira da infeção préssintomática. A proporção total de infeção assintomática foi de 16% (95% IC 12% a 20%).²

Os testes comunitários por RT-PCR de toda a aldeia de Vo em Itália, em dois períodos distintos, demonstraram uma prevalência global de infeção de 2,6% no início do confinamento e de 1,2% no final do confinamento, sendo assintomáticas 43% de todas as infeções.³ Os dados do rastreio dos profissionais de saúde (PS), onde a infeção não reconhecida pode ter consequências significativas para a transmissão nosocomial, sugerem uma prevalência global reduzida de infeção assintomática. O rastreio assintomático de profissionais de saúde num hospital de Londres revelou uma prevalência de 7% no final de março, reduzindo para 1% no final de abril.⁴ Em Cambridge, Reino Unido, o rastreio de 1032 profissionais de saúde, em abril, revelou 30 (3%) casos positivos, dos quais apenas 5 foram considerados verdadeiramente assintomáticos.⁵

Provavelmente, o mais comparável ao ambiente dos navios de cruzeiro são os dados provenientes dos surtos de lares de idosos, revelando uma elevada prevalência de infeção. Num lar em Washington, EUA, com 89 residentes, 55 (62%) testaram positivo durante 3 semanas.⁶ Embora 27 (49%) estivessem assintomáticos na altura dos testes, apenas 3 (5%) permaneceram assintomáticos durante o período de seguimento observado pelo menos durante 7 dias. Além disso, durante o seguimento de 96 casos assintomáticos do cruzeiro Diamond Princess, 11 indivíduos desenvolveram sintomas subsequentemente, com um maior risco de doença em doentes mais idosos.⁷

A transmissão subsequente de infeção assintomática foi descrita pela primeira vez na China, onde um caso índice transmitiu a infeção a cinco membros de uma família, apesar de se ter mantido sempre assintomático.⁸ A investigação de 30 doentes no Vietname revelou cargas virais inferiores naqueles que se encontravam assintomáticos, tendo a investigação epidemiológica revelado pelo menos 3 casos que tinham sido contraídos através de contacto com fontes assintomáticas.⁹ Em Guangzhou, China, 4950 contactos de 129 casos confirmados, incluindo 8 casos assintomáticos, foram rastreados regularmente com RT-PCR a cada 2 dias.¹⁰ Uma única infeção (0,3%) ocorreu em 305 contactos dos casos assintomáticos em comparação com 116 infeções (5%) em 2305 contactos de casos sintomáticos.

O surto num navio de cruzeiro descrito por Ing *et al* levanta outra questão interessante relacionada com a variabilidade do risco de transmissão a partir de casos infetados (o parâmetro de sobredispersão), em que, por vezes, um elevado número de casos secundários surge de uma suposta única fonte.¹¹ A modelação matemática estimou que 80% das transmissões secundárias podem decorrer de muito poucos casos, até 10%.¹² Se se demonstrar que os casos assintomáticos contribuem para estes eventos de "superdispersão", então qualquer intervenção na avaliação de um surto deverá ser capaz de reconhecer e gerir tais casos.

As implicações mais amplas do rastreio de infeção assintomática como parte de intervenções eficazes para reduzir a transmissão de SARS-CoV-2 são particularmente relevantes à medida que os governos im-

plementam estratégias para implementar medidas de confinamento. A atual base da intervenção assenta na identificação da infeção, no isolamento dos casos, na implementação de medidas de controlo da infeção e no rastreio dos contactos. A realização indiscriminada de testes de RT-PCR em massa a grupos assintomáticos requer uma cuidadosa consideração da capacidade de testes laboratoriais e interpretação dos resultados dos testes no contexto de uma positividade RT-PCR não infecciosa e prolongada em convalescença.¹³

No entanto, em cenários de surto, onde foi repetidamente demonstrada uma elevada prevalência de infeção assintomática a partir de dados de prevalência pontual, o rastreio em massa representa uma ferramenta valiosa para identificar casos assintomáticos (incluindo paucissintomáticos, e préssintomáticos), que de outra forma não seriam identificados. Isto poderia ser aplicado em lares, navios de cruzeiro, em surtos hospitalares ou outros agrupamentos comunitários, a fim de interromper de imediato e completamente as cadeias de transmissão. Determinar se a transmissão de casos assintomáticos é um acontecimento raro ou um fator significativo de propagação do SARS-CoV-2 deve ser uma prioridade de investigação, permitindo tanto aos navios de cruzeiro como aos governos traçar um caminho em segurança para pôr fim a esta pandemia.

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Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; externally peer reviewed.

Data availability statement No data are available. This article is made freely available for use in accordance with BMJ's website terms and conditions for the duration of the covid-19 pandemic or until otherwise determined by BMJ. You may use, download and print the article for any lawful, non-commercial purpose (including text and data mining) provided that all copyright notices and trade marks are retained. © Author(s) (or their employer(s)) 2020. No commercial re-use. See rights and permissions. Published by BMJ



To cite Keeley AJ, Evans CM, de Silva TI. Thorax 2020;75:621–622.

Received 4 June 2020

Accepted 6 June 2020

Published Online First 24 June 2020



► <http://dx.doi.org/10.1136/thoraxjnl-2020-215091>

Thorax 2020;75:621–622.

doi:10.1136/thoraxjnl-2020-215337

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LAMA | LABA | ICS



1 INALAÇÃO



1 VEZ AO DIA



1 DISPOSITIVO

ELEBRATO
FUROATO DE FLUTICASONA | UMECLIDÍNIO | VILANTEROL | ELLIPTA
ELE RESPIRA

Referências: 1. Van der Palen J et al. NPJ Prim Care Respir Med 2016 26:16079 2. Lipson DA et al. N Engl J Med 2018 378:1671-1680 3. RCM Elebrato Ellipta março 2019
DPOC: Doença pulmonar obstrutiva crônica; ICS: Corticosteroide inalado; LABA: Agonista β_2 de longa ação; LAMA: Antagonista muscarínico de longa ação.

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