

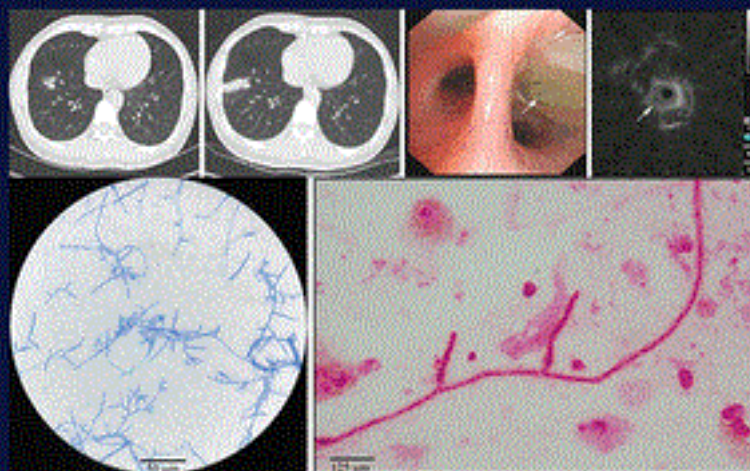
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Editorial

Ao terminar a primeira metade do ano de 2023, estamos de volta com mais um número da edição em língua Portuguesa de artigos selecionados das revistas *Thorax* e *Archives of Disease in Childhood*.

Esta primeira parte do ano tem sido dominada pelas notícias frequentes sobre as dificuldades crescentes do Serviço Nacional de Saúde Português, sobretudo no que respeita ao recrutamento e retenção de recursos humanos, ao constante subfinanciamento e aos problemas organizacionais e estruturais. Apesar das repetidas declarações de intenções reformistas, ainda não se vislumbram soluções que garantam um ressurgimento e revalorização do SNS. Como profissionais de saúde e como cidadãos, não podemos deixar de manifestar a nossa preocupação com esta situação.

Entretanto, a importantíssima iniciativa do Governo para melhorar a regulação e controlo sobre o uso de produtos do tabaco não parece estar a encontrar apoios suficientes entre os deputados da Assembleia da República, correndo-se o risco de se perder uma oportunidade de usar a legislação como um dos instrumentos mais importantes para diminuir o impacto negativo para a saúde pública do consumo de produtos de tabaco. Esperamos que ainda seja possível conseguir uma legislação que coloque Portugal a par da maioria dos restantes países da Europa no que respeita à regulação do consumo destas substâncias.

Neste número da Revista, chamamos a sua atenção para alguns artigos.

O primeiro é o artigo “Aptidão cardiopulmonar em crianças com asma vs crianças saudáveis” e teve como objetivo avaliar a aptidão cardiopulmonar das crianças com asma, por comparação aos controlos saudáveis, e identificar os parâmetros clínicos e da prova de esforço cardiorrespiratória associados ao volume de oxigénio máximo na asma infantil. O estudo conclui que a adequação cardiopulmonar nas crianças com asma estava moderada, mas significativamente alterada, quando comparada com as crianças saudáveis. O segundo artigo intitula-se “Avaliação do tratamento formal do tabagismo e da interrupção do hábito de fumar em fumadores duais de cigarros combustíveis e cigarros eletrónicos”, um estudo longitudinal em adultos em ambulatório, em que foi avaliada a relação entre a utilização de cigarros eletrónicos (com ou sem tratamento formal do tabagismo) e a prevalência da interrupção do hábito de fumar. Os resultados sugerem que os utilizadores duais de cigarros combustíveis e eletrónicos beneficiam de um tratamento formal de tabagismo.

Sugere-se ainda a leitura do artigo “Utilizar uma aplicação para smartphone mantém a atividade física na sequência da reabilitação pulmonar em pacientes com DPOC: um ensaio aleatorizado com controlo” que conclui que um programa abrangente de utilização de uma App após RP manteve a AF e melhorou os sintomas dos pacientes com DPOC aos 6 meses. A App poderá ser uma ferramenta acessória importante para os cuidados às pessoas com DPOC.

Os restantes artigos merecem igualmente uma leitura atenta. Esperamos que a presente seleção seja do agrado dos leitores.

Desejamos a todos umas boas férias e regressaremos em breve com novas escolhas.

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RESUMO

Objetivos Avaliar, com uma prova de esforço cardiorrespiratória (PECR), a aptidão cardiopulmonar das crianças com asma, por comparação aos controlos saudáveis, e para identificar os parâmetros clínicos e de PECR associados ao volume de oxigénio máximo (VO_{2max}) na asma infantil.

Conceção Este estudo transversal controlado foi levado a cabo em laboratórios PECR de dois centros de cuidados pediátricos terciários. Os previsores de VO_{2max} foram determinados utilizando uma análise multivariável.

Resultados Um total de 446 crianças (144 no grupo de asmáticos e 302 no grupo dos sujeitos saudáveis) realizaram um PECR completo. O VO_{2max} médio foi significativamente mais baixo nas crianças com asma do que nos controlos [$38,6 \pm 8,6$ vs. $45,3 \pm 7,5$ mL/kg/min; diferença absoluta (dif. abs.) de $-4,9$ mL/kg/min; IC 95 %, de $-6,5$ a $-3,3$ mL/kg/min; $p < 0,01$] e representou 94 % $\pm$ 9% e 107% $\pm$ 17% dos valores previstos, respetivamente (dif. abs. -13%; IC 95%, -17 a -9%; $p < 0,01$). A proporção de crianças com um VO_{2max} deficiente foi quatro vezes mais elevada no grupo dos asmáticos (24% vs. 6%, $p < 0,01$). A deficiente eficiência ventilatória com declive VE/CO_2 aumentado e a baixa reserva respiratória foram mais marcadas no grupo dos asmáticos. A proporção de crianças com um limiar anaeróbico ventilatório (LAN) reduzido, indicador de descondicionamento físico, foi três vezes mais elevada no grupo dos asmáticos (31% vs. 11%, $p < 0,01$). O deficiente VO_{2max} esteve associado ao género feminino, com um índice de massa corporal elevado (IMC), FEV₁, LAN reduzido e reserva respiratória elevada.

Conclusão A adequação cardiopulmonar nas crianças com asma estava moderada mas significativamente alterada quando comparado com as crianças saudáveis. Um VO_{2max} reduzido esteve associado ao género feminino, ao IMC elevado e à função pulmonar.

Número de registo do ensaio NCT04650464.

BACKGROUND

Asthma is the most common paediatric chronic disease worldwide, leading to frequent hospital admissions and school absenteeism.¹ Paediatric asthma has become a serious public health issue and current management mainly relies on symptom control in order to ensure to children with asthma a normal quality of life.² Asthma is characterised by chronic inflammation of lower airways, marked by expiratory airflow limitation and repeated respiratory symptoms, including wheezing, shortness of breath, chest tightness and cough.³ Asthma symptoms, associated with patient's fear of exertional dyspnoea, may limit the ability to be physically active, leading to a sedentary lifestyle, and ultimately affect child's quality of life.⁴

In 1980, the WHO stated that functional capacity explorations best reflected the impact of chronic disease on health-related quality of life.⁵ Therefore, cardiopulmonary exercise test (CPET) with maximum oxygen uptake (VO_{2max}) assessment has become the reference functional examination

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Asthma is the most common chronic disease in children worldwide.
- Asthma respiratory symptoms may limit the patient's ability to be physically active, potentially resulting in a sedentary lifestyle and an impaired quality of life.

WHAT THIS STUDY ADDS

- Cardiopulmonary fitness in children with asthma is moderately but significantly altered in comparison with healthy children.
- VO_{2max} is impaired in a quarter of children with asthma, with patterns of physical deconditioning in a third of them.
- Impaired VO_{2max} is associated with female gender, high body mass index and the degree of obstructive lung disease.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- The use of cardiopulmonary exercise test (CPET) is of interest in the follow-up of paediatric asthma.
- CPET identifies children with asthma most at risk of physical deconditioning.
- CPET contributes to promote physical activity and cardiopulmonary rehabilitation in childhood asthma.

in cardiorespiratory diseases,⁶ first in adult population, and more recently in paediatric population. Indeed, in children, VO_{2max} is associated with patient-reported outcomes, such as health-related quality of life.⁷ The existence of an impaired cardiopulmonary fitness in children may be related to various limiting factors, such as cardiac limitation, ventilatory limitation, physical deconditioning or even psychological barriers to physical activity.⁸

Most paediatric studies on cardiopulmonary fitness have enrolled healthy children, children with cardiac conditions⁹ or children with cystic fibrosis.¹⁰

By contrast, the level of VO_{2max} in children with asthma from large paediatric CPET cohorts has been scarcely reported, especially in comparison with healthy children.^{11–14} Previous reports suggested that ventilatory exercise limitations could be related to the severity of bronchial obstruction,^{15 16} but the predictors of VO_{2max} and the level of physical deconditioning in children with asthma remain unclear.^{17 18}

In this study, we aimed to evaluate the cardiopulmonary fitness, assessed by a CPET, in a large cohort of children with asthma, and to compare

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the results to healthy controls. We also intended to identify the predictors of $\text{VO}_{2\text{max}}$ in children with asthma.

METHODS

Study design and population

This cross-sectional controlled study was carried out from January 2015 to December 2019 in two tertiary care paediatric centres (Montpellier University Hospital and Saint-Pierre-Institute, France). Children aged 5–18 years old, and measuring at least 120 cm, were recruited in two paediatric CPET laboratories. Children with absolute contraindications for CPET were not eligible.⁹

Two groups were identified: children with asthma and healthy control children.

The asthma group consisted of children followed up for asthma and referred to one of the two centres by paediatricians, pulmonologist or general practitioners. The level of asthma severity was assessed by the therapeutic burden from the Global Initiative for Asthma (GINA) classification.³ From patients' interviews, the absence of any physical activity, apart from physical education at school, was indicative of sedentary lifestyle. Also, exercise-related symptoms (chest pain or excessive dyspnoea) were reported.

As in our previous similar CPET controlled paediatric studies, the control group consisted of children referred for non-severe functional symptoms linked to exercise (murmur, palpitation or dyspnoea) or for medical sports certificate.^{9 19 20} These children were classified as controls after a completely normal check-up, including physical examination, ECG, echocardiography and spirometry. Children with any chronic disease, medical condition (cardiac, neurologic, respiratory, muscular or renal), or medical treatment, and those requiring any further specialised medical consultation were not eligible.

Paediatric laboratory functional tests: spirometry and CPET

Functional tests procedures in both centres were harmonised before the study started. We used the Quark CPET calibrated gas analyser (Cosmed Srl., Pavia di Albano, Italy).

Spirometry tests were repeated at least three times to ensure reproducibility,²¹ and the results of FEV1, FVC and FEV1/FVC ratio (FEV1/FVC%) were expressed in Z-scores.²²

Both centres used the same CPET paediatric cycle ergometer protocol to obtain a homogeneous incremental overall duration between 8 and 12 min. Whenever the $\text{VO}_{2\text{max}}$ did not reach a plateau, which is common in children, the peak VO_2 was collected.⁸ $\text{VO}_{2\text{max}}$ values were normalised as percentage of the predicted $\text{VO}_{2\text{max}}$.²³ A $\text{VO}_{2\text{max}} < 80\%$ of predicted values indicated impaired cardiopulmonary fitness.²⁴

The ventilatory anaerobic threshold (VAT) was measured using the V-slope method.²⁵ A decreased VAT $< 55\%$ of predicted $\text{VO}_{2\text{max}}$ values was in favour of physical deconditioning.^{9 26} The ventilatory efficiency (VE/VCO_2 slope) was measured from the beginning of incremental exercise (after the warm-up period) to maximum exercise.²⁷ A VE/VCO_2 slope > 30 indicated impaired ventilatory efficiency.²⁷ The maximal voluntary ventilation, the breathing reserve (BR), the oxygen pulse, the oxygen uptake efficiency slope (OUES)²⁸ and the main respiratory variables at maximal exercise were collected (detailed CPET protocol and parameters available in online supplemental material).

Statistical analysis

The study population was described using means and SD or median and interquartiles (Q1–Q3) for quantitative variables, and with frequencies for categorical variables. The continuous variable distributions were tested using the Shapiro-Wilk test. Quantitative variables were compared using Student's t-test when the distribution was Gaussian and using the Mann-Whitney test otherwise. For qualitative variables, groups were compared using the χ^2 test or Fisher's exact test.

Depending on the distribution of variables, correlations were performed using Pearson's or Spearman's coefficients.

We compared CPET parameters between asthma and control groups with generalised linear models adjusted on gender, age and body mass index (BMI).

A linear model was used to compare the variation of $\text{VO}_{2\text{max}}$ per year between asthma and control groups. This analysis was stratified on gender because the interaction between age and gender was significant ($p < 0.01$). The results were illustrated with a scatter plot and their regression line for each group. On these figures, the p value represented the slope comparison between asthma and control groups.

Table 1 Main demographic, spirometry and clinical data

Demographic data				
Variables	Asthma (N=144)	Controls (N=302)	Abs. diff. (95% CI)	P value
Age (years)	11.4±2.8	11.1±2.6	0.3 (−0.2 to 0.8)	0.41
Height (cm)	149.5±14.7	150.0±16.0	−0.4 (−3.5 to 2.7)	0.80
Weight (kg)	44.1±15.0	42.2±13.3	1.9 (−0.8 to 4.7)	0.32
BMI (kg/m ²)	19.3±4.0	18.3±2.9	1.0 (0.3 to 1.7)	0.05
Male	88 (61)	172 (57)	4.2 (−5.6 to 13.9)	0.41
Spirometry data				
FEV1 (Z-score)	−0.7±1.4	0.5±1.1	−1.2 (−1.4 to −0.9)	< 0.01
FVC (Z-score)	−0.2±1.4	0.5±1.3	−0.8 (−1.0 to −0.5)	< 0.01
FEV1/FVC (Z-score)	−0.7±1.4	0.0±1.2	−0.7 (−1.0 to −0.4)	< 0.01
Clinical data				
Regular controller treatment	101 (70)			
Step GINA				
1	43 (30)	—		—
2	11 (8)	—		—
3	41 (28)	—		—
4	44 (31)	—		—
5	5 (3)	—		—
Step GINA: severe (4-5)	49 (34)	—		—
Associated pathology	21 (15)	—		—
Sedentary lifestyle	44 (33)	—		—
Symptoms during daily exercise	110 (76)	—		—

Values are mean±SD or N (%).

Abs. diff., absolute difference; BMI, body mass index.

Table 2 Cardiopulmonary exercise test (CPET) parameters: comparison between asthma and control groups

Variables	Raw CPET values				Adjusted CPET values*			
	Asthma	Controls	Abs. diff.(95% CI)†	P value	Asthma	Controls	Abs. diff. (95% CI)	P value
VO _{2max} (mL/kg/min)	38.6±8.6	43.5±7.5	−4.9 (−6.5 to −3.3)	<0.01	38.5±5.9	42.6±5.9	−4.1 (−5.2 to −2.9)	<0.001
Percent-predicted VO _{2max} (%)	94±19	107±17	−13 (−17 to −9)	<0.01	96±15	106±15	−10 (−13 to −7)	<0.001
Low VO _{2max} <80%	35 (24)	19 (6)	18 (10 to 26)	<0.01	—	—	—	—
Maximal load (watt)	115 (95–155)	120 (75–160)	0 (−10 to 20)	0.54	120.0±42.0	112.2±41.7	7.8 (−0.5 to 16.1)	0.06
VAT (mL/kg/min)	26.7±6.9	29.1±6.4	−2.4 (−3.7 to −1.1)	<0.01	26.8±5.1	28.4±5.1	−1.6 (−2.7 to −0.6)	<0.01
Percent-predicted VAT (%)	65±16	71±14	−6 (−9 to −3)	<0.01	67±13	71±13	−4 (−6 to −1)	<0.01
Low VAT <55%	44 (31)	34 (11)	19 (11 to 28)	<0.01	—	—	—	—
BR (%)	23 (11–34)	30 (19–39)	−7 (−10 to −4)	<0.01	22.0±15.8	29.3±15.7	−7.2 (−10.4 to −4.1)	<0.001
Vt (mL/kg)	28.8±7.2	30.4±5.9	−1.6 (−2.9 to −0.2)	0.02	29.0±5.4	30.0±5.3	−1.0 (−2.0 to 0.1)	0.08
Respiratory rate (breaths/min)	50.5±10.2	52.0±10.2	−1.6 (−3.6 to 0.5)	0.13	50.4±10.0	51.9±9.9	−1.5 (−3.5 to 0.5)	0.14
PetCO ₂ (mm Hg)	34.8 (32.0–38.0)	33.5 (31.0–35.8)	1.4 (0.5 to 2.2)	<0.01	34.8±4.3	33.6±4.3	1.3 (0.4 to 2.1)	<0.01
VEQO ₂	34.4 (31.3–39.1)	34.9 (31.1–38.5)	0.0 (−1.2 to 1.1)	0.98	35.6±5.7	35.4±5.6	0.2 (−0.9 to 1.3)	0.73
VEQO ₂	30.1 (27.9–33.5)	31.2 (29.0–33.7)	−0.8 (−1.5 to 0.0)	0.05	30.9±3.9	31.5±3.8	−0.6 (−1.4 to 0.1)	0.10
Peak heart rate (beats/min)	185 (178–191)	187 (181–193)	−3 (−5 to −1)	<0.01	183.9±11.1	187.5±11.1	−3.6 (−5.8 to −1.4)	<0.01
Percent-predicted peak HR (%)	84 (81–87)	90 (87–93)	−6 (−7 to −5)	<0.01	84±5	90±5	−6 (−7 to −5)	<0.001
Peak oxygen pulse (mL/beat)	8.5 (7.2–10.2)	9.1 (7.4–11.0)	−0.5 (−1.0 to −0.0)	0.04	8.5±1.9	9.6±1.9	−1.2 (−1.6 to −0.8)	<0.001
RER	1.2 (1.1–1.2)	1.1 (1.1–1.2)	0.0 (0.0 to 0.1)	<0.01	1.2±0.1	1.1±0.1	0.1 (0.0 to 0.1)	<0.01
VE/VCO ₂ slope	30.8 (28.7–33.3)	29.6 (26.6–32.1)	1.5 (0.7 to 2.2)	<0.01	31.1±3.9	29.6±3.8	1.5 (0.7;2.3)	<0.001
VE/VCO ₂ slope >30	90 (63)	136 (45)	17 (8 to 27)	<0.01	—	—	—	—
OUES	1840.0 (1488.5–2225.0)	1739.5 (1383.0–2225.0)	82.0 (−50.0 to 215.0)	0.22	1772.7±438.4	1852.1±433.3	−79.4 (−181.1 to 22.3)	0.13
OUES/kg	43.5 (37.1–52.9)	44.1 (38.6–50.1)	0.2 (−2.4 to 2.7)	0.91	44.7±8.6	43.9±8.5	0.8 (−1.1 to 2.8)	0.41

Values are mean±SD or median (Q1–Q3) or N (%).

Significant values are marked in bold.

*Adjusted on age, gender and BMI.

†Hodges-Lehmann method was used to calculate the absolute difference of the median with its CI.

Abs. diff., absolute difference; BR, breath reserve; HR, heart rate; OUES, oxygen uptake efficiency slope; PetCO₂, partial pressure of end tidal CO₂; Oxygen pulse, VO₂ ÷ heart rate; RER, respiratory exchange ratio (VCO₂ ÷ VO₂); VE/VCO₂ slope, the minute ventilation/carbon dioxide production slope; VAT, ventilatory anaerobic threshold; VEQO₂, ventilatory equivalent for carbon dioxide: ratio of the volume of air ventilating the lungs to the volume of carbon dioxide produced; VEQO₂, ventilatory equivalent for oxygen: ratio of the volume of gas expired per minute to the volume of oxygen consumed per minute; VO_{2max}, maximum oxygen uptake; Vt, tidal volume.

A multiple linear regression was used to identify the explanatory factors for VO_{2max} in the asthma group. The clinically relevant variables (such as the BR to explore ventilatory limitation, the VAT to reflect muscular deconditioning and usual spirometric parameters), some clinically relevant interactions (such FEV1*BMI or VAT*BMI and BR*BMI) and the variables with a p value ≤0.2 in

the univariate analysis were included in the model. The final model was obtained using an upward selection based on the corrected Akaike information criterion and with an exit threshold of 0.10. The normality of residuals in the final model was tested using the Shapiro-Wilk test.

The statistical significance was set at 0.05 and analyses were performed using Statistical Analysis Systems Enterprise Guide V4.3 (SAS Institute).

Ethics

The study was conducted in compliance with the Good Clinical Practices protocol and Declaration of Helsinki principles. Informed consent was obtained from all parents or legal guardians.

RESULTS

Population

A total of 446 children were included in the study (centre 1, n=236; centre 2, n=210): 144 in the asthma group and 302 in the control group. No family refused to participate.

There was no difference between the two centres in terms of demographic data and asthma severity assessed by the therapeutic burden from the GINA classification (p=0.35). Moreover, asthmatic and control children were similar, except for anthropometric and spirometry data (table 1). No adverse events were reported during the exercise tests.

In the asthma group, 70% of patients had a specific asthma treatment and one-third was classified in the step 4 or 5 of GINA classification. FEV1, FVC and ratio FEV1/FVC were significantly

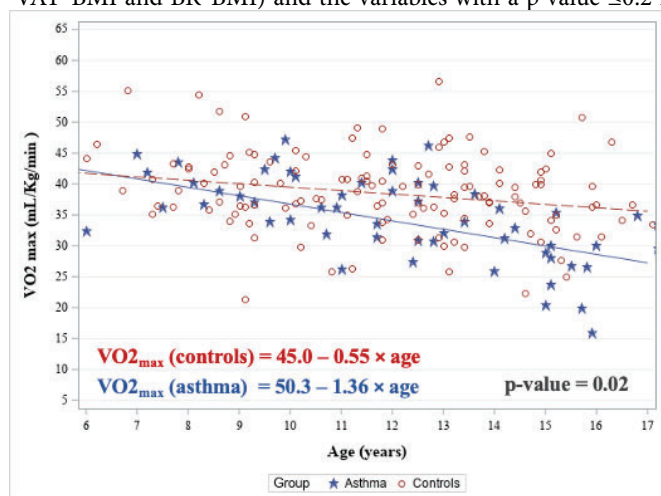


Figure 1 Relationship between age and VO_{2max} in female subjects. Equations of the VO_{2max} models according to age for asthma and control groups were reported. The p value illustrates the comparison between the two slopes.

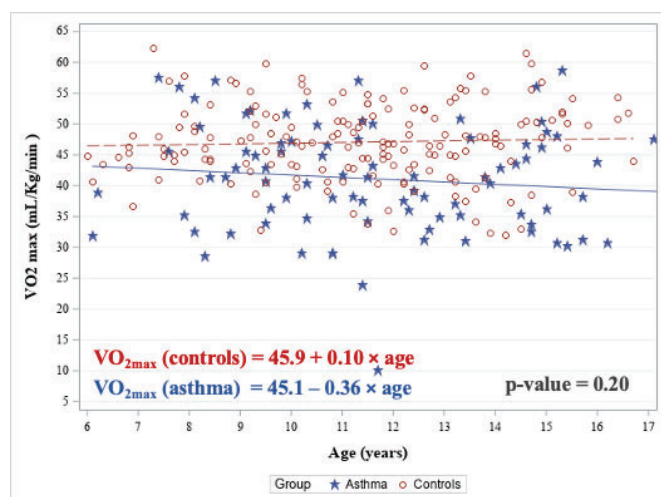


Figure 2 Relationship between age and VO_{2max} in male subjects. Equations of the VO_{2max} models according to age for asthma and control groups were reported. The p value illustrates the comparison between the two slopes.

lower in the asthma group. Most patients with asthma felt chest pain or excessive dyspnoea during daily exercise, and one-third had a sedentary lifestyle.

CPET results

All enrolled children performed a maximal exercise test and both groups were similar in terms of maximum load.

In the control group, the mean VO_{2max} per body weight was normal (43.5 ± 7.5 mL/kg/min), representing $107\% \pm 17\%$ of the predicted values. In the asthma group, the mean VO_{2max} per body weight was good, overall (38.6 ± 8.6 mL/kg/min), representing $94\% \pm 19\%$ of the predicted values, but was significantly lower than

in healthy controls, with an absolute difference of -4.9 mL/kg/min and a 95% CI of $(-6.5$ to $-3.3)$ mL/kg/min ($p < 0.01$). Expressed in VO_{2max} percent-predicts, this represented an absolute difference of -13% (95% CI $(-17$ to $-9)\%$; $p < 0.01$). We found similar results after adjustment on age, gender and BMI. The proportion of children with an impaired VO_{2max} was four times higher in the asthma group than in the control group (24% vs 6%, $p < 0.01$, respectively).

The VAT was significantly lower in the asthma group (26.7 ± 6.9 vs 29.1 ± 6.4 mL/kg/min), with an absolute difference of -2.4 mL/kg/min (95% CI $(-3.7$ to $-1.1)$ mL/kg/min; $p < 0.01$). Expressed in VO_{2max} percent-predicts, this represented $65\% \pm 16\%$ of predicted VO_{2max} and an absolute difference of -6% (95% CI $(-9$ to $-3)\%$; $p < 0.01$). The proportion of children with a decreased VAT $< 55\%$ was three times higher in the asthma group (31% vs 11%, $p < 0.01$).

In the asthma group, the VE/VCO_2 slope, the proportion of children with an impaired ventilatory efficiency and the $PetCO_2$ were higher. The BR, V_t and oxygen pulse values were significantly lower in the asthma group. No significant differences were observed for respiratory rate, ventilatory equivalents and OUES values.

After adjustment of CPET parameters on age, gender and BMI, similar differences between asthma and control groups were observed for VO_{2max} , VAT, VE/VCO_2 slope and BR (table 2).

In female children, VO_{2max} decreased significantly faster with age in the asthma group than in controls (-1.36 mL/kg/min per year, 95% CI $(-1.87$ to $-0.84)$ vs -0.55 mL/kg/min per year, 95% CI $(-0.96$ to $-0.15)$, $p = 0.02$, respectively) (figure 1). We observed a decrease of 1.95% of predicted VO_{2max} per year of age in girls with asthma. No difference was observed in male subjects (-0.36 mL/kg/min per year, 95% CI $(-1.04$ to $0.33)$ vs 0.10 mL/kg/min per year, 95% CI $(-0.27$ to $0.48)$, $p = 0.20$, respectively, for asthma and control groups) (figure 2).

Predictors of VO_{2max} in the asthma group

A lower VO_{2max} was associated with female gender, high BMI, low FEV1, low VAT and high BR, in both univariate and multivariate

Table 3 Clinical determinants of VO_{2max} in the asthma group (linear regression)

Variables				Univariate analysis		Multivariable analysis (N=144)	
		N	r	β (95% CI)	P value	β (95% CI)	P value
Age (years)*		144	-0.3	-0.85 (-1.34 to -0.36)	<0.001	—	—
BMI (%)*		144	-0.52	-0.13 (-0.17 to -0.09)	<0.0001	-0.07 (-0.09 to -0.05)	<0.0001
FEV1 (Z-score)*		144	0.15	0.91 (-0.08 to 1.90)	0.07	0.86 (0.39 to 1.32)	<0.001
FVC (Z-score)*		144	0.18	1.09 (0.08 to 2.10)	0.04	—	—
FEV1/FVC (Z-score)		144	-0.03	-0.20 (-1.20 to 0.80)	0.69	—	—
VAT (mL/kg/min)*		144	0.86	1.08 (0.97 to 1.18)	<0.0001	0.87 (0.76 to 0.98)	<0.0001
BR (%)*		144	-0.18	-0.09 (-0.17 to -0.01)	0.04	-0.08 (-0.12 to -0.05)	<0.0001
		N	Mean $\pm$ SD				
Gender*	Female	56	34.6 $\pm$ 6.9	-6.44 (-9.17 to -3.72)	<0.0001	-2.11 (-3.50 to -0.73)	<0.01
	Male	88	41.1 $\pm$ 8.8	—	—	—	—
Regular controller treatment	No	43	38.3 $\pm$ 8.4	-0.38 (-3.50 to 2.74)	0.81	—	—
	Yes	101	38.7 $\pm$ 8.8	—	—	—	—
Step GINA severe	No	95	38.9 $\pm$ 8.9	1.08 (-1.93 to 4.08)	0.48	—	—
	Yes	49	37.8 $\pm$ 8.1	—	—	—	—
Montelukast treatment	No	116	38.5 $\pm$ 9.1	-0.40 (-4.01 to 3.20)	0.83	—	—
	Yes	28	38.9 $\pm$ 6.7	—	—	—	—
Sedentary lifestyle*	No	88	40.1 $\pm$ 8.7	4.97 (1.84 to 8.10)	<0.01	—	—
	Yes	44	35.2 $\pm$ 8.3	—	—	—	—
Symptoms during daily exercise	No	34	37.7 $\pm$ 8.8	-1.09 (-4.44 to 2.27)	0.52	—	—
	Yes	110	38.8 $\pm$ 8.6	—	—	—	—
Associated pathology	No	123	38.7 $\pm$ 8.7	1.11 (-2.92 to 5.15)	0.59	—	—
	Yes	21	37.6 $\pm$ 8.1	—	—	—	—

Values are correlation coefficients (r) or means $\pm$ SD.

*Candidate variables for multivariable analysis. Variables associated with VO_{2max} in both univariate and multivariable analyses are marked in bold.

β , adjusted β ; BMI, body mass index; BR, breath reserve; β , crude β ; FEV1/FVC, Tiffeneau index; VAT, ventilatory anaerobic threshold; VO_{2max} , maximum oxygen uptake.

able analyses (table 3). However, no association was found between VO_{2max} and the level of asthma severity from the GINA classification. There was no significant interaction between BMI with FEV1, VAT and BR. The final multivariate model explained 82% of the variability of VO_{2max} in the asthma group.

DISCUSSION

From a paediatric cohort of 446 subjects, this multicentre controlled study provided values and predictors of cardiopulmonary fitness in 144 children with asthma compared with 302 healthy controls.

Overall, the cardiopulmonary fitness of children with asthma was good ($VO_{2max} > 90\%$). However, their VO_{2max} was lower than that of healthy subjects, with a mean difference of 13% between their respective percent-predict values. Moreover, the VO_{2max} was impaired in nearly one-fourth of children with asthma, which was four times higher than in healthy subjects. The VO_{2max} decrease was associated with lower FEV1. Previous reports on cardiopulmonary fitness in children with asthma are controversial,²⁹ as some studies found VO_{2max} values similar to healthy controls,^{13 14} whereas others found lower VO_{2max} values in children with asthma.^{12 30} However, those studies enrolled small numbers of subjects and used heterogeneous CPET protocols. Unsurprisingly, the VO_{2max} was lower in children with high BMI, as adipose tissue does not consume oxygen, as well as in girls, reflecting the well-known gender differences in muscle mass and adipose tissue.^{9 31} Exercise-induced symptoms may be associated with misdiagnosis of asthma in overweight subjects.³² Therefore, in this study, CPET parameters' comparisons used generalised linear models adjusted not only on gender and age, but also on BMI, in order to determine the impact of paediatric asthma on aerobic fitness.

Interestingly, the results of this study suggest the existence of an early onset of physical deconditioning in childhood asthma. Indeed, the VAT was a predictor of VO_{2max} and nearly one-third of children with asthma had low VAT values, which was three times higher than in healthy controls. Moreover, asthma severity, as assessed by the GINA classification, was not associated with VO_{2max} . Nevertheless, few subjects with severe asthmatic forms were included in this study.

In this cohort, most children with asthma felt chest pain or excessive dyspnoea during daily exercise, and one-third had a sedentary lifestyle. In the literature, barriers to physical activity in children with asthma have been mainly related to an altered self-perception of physical capacity^{16 18} and, to a lesser extent, to insufficient asthma control, dynamic hyperinflation and air trapping during effort, or exercise-induced bronchoconstriction.^{33 34}

Indeed, some children may limit their activities for fear of experiencing symptoms during exercise.³⁵ They gradually adopt a sedentary lifestyle, responsible for increased symptoms during exercise, which will ultimately aggravate the vicious circle of physical deconditioning. This is supported in this study by the VO_{2max} decrease over time in the asthma group (1.36 mL/kg/min/year in girls and 0.36 mL/kg/min/year in boys). Furthermore, this study provided original data on ventilatory parameters during exercise in childhood asthma. Previous studies failed to identify any significant differences in exercise ventilatory parameters between children with and without asthma.^{15 36} Globally, children with asthma were prone to some degree of ventilatory inefficiency, as reflected by the VE/VCO₂ slope. Previous reports have described the hyperventilation syndrome³⁷ as indicative of ventilatory limitation in children with asthma,³⁸ but this has not been observed in our study, where higher PetCO₂ values at the end of exercise have been observed.

Interestingly, in children with asthma from our cohort, a higher BR was a predictor of a lower VO_{2max} , suggesting that exercise limitation in childhood asthma does not only rely on the respiratory impairment but also includes a certain degree of physical deconditioning.

As a result, the use of CPET in childhood asthma follow-up provides a comprehensive assessment of cardiopulmonary fitness and evaluates the impact of the obstructive lung disease on physical

capacity. Ultimately, the CPET identifies the patients most at risk of physical deconditioning in this population, and therefore could be the first step of exercise rehabilitation in childhood asthma. Unfortunately, cardiopulmonary rehabilitation programmes in asthma have been scarcely developed, despite preliminary positive results in small studies focused on physical training.³⁹ Nevertheless, previous studies have highlighted the benefits of regular physical activity in asthma in terms of disease control, lung function and mental health.³⁰ Moreover, regular physical activity is highly recommended by GINA in the global management of asthma.³ In a near future, evaluation and promotion of physical activity in children with asthma and impaired physical fitness could therefore be supported by structured rehabilitation programmes, including both exercise training and patient education, as recently reported in other paediatric conditions.⁴⁰

Study limitations

This study was performed in tertiary care centres, therefore, children with more severe asthma status may have been enrolled, which may not represent asthmatic children in the general population. Data on asthma control were not available but would have been of great interest in the perspective of further patients' education. Moreover, further work should be carried out to evaluate the impact of exercise-induced bronchospasm and dynamic hyperinflation on cardiopulmonary fitness in paediatric asthma.

CONCLUSION

Cardiopulmonary fitness in children with asthma was moderately but significantly altered, in comparison with healthy children, and VO_{2max} was impaired in one-fourth of children with asthma. A decreased VO_{2max} was associated with female gender, high BMI, low VAT and low FEV1. Nearly one-third of children with asthma had low VAT values, suggesting an early onset of physical deconditioning. Children with asthma were prone to ventilatory inefficiency during exercise. The use of CPET in the follow-up of paediatric asthma evaluates the impact of the obstructive lung disease on cardiopulmonary fitness and identifies the children most at risk of physical deconditioning. Further work will have to determine the interest of CPET in promotion of physical activity and cardiopulmonary rehabilitation for childhood asthma.

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ARTIGO ORIGINAL

Condição pós-COVID-19 aos 6 meses e vacinação COVID-19 em crianças e jovens não hospitalizados

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RESUMO

Objetivos Descrever a saúde física e mental das crianças e jovens (CJ) 6 meses após infecção por SARS-CoV-2 e explorar se ocorre variação devido à vacinação contra a COVID-19.

Desenho Uma coorte de pessoas não hospitalizadas, com idades compreendidas entre os 11 e os 17 anos, com infecção por SARS-CoV-2 confirmada por teste PCR e com PCR negativos emparelhadas no momento do convite para o estudo por idade, sexo, região e data do teste, que concluíram os questionários 6 meses após o teste PCR. O questionário incluiu 21 sintomas e escalas padronizadas (p. ex., EQ-5D-Y e Escala de Fadiga de Chalder).

Resultados 6407 CJ com teste positivo e 6542 com teste negativo concluíram o questionário aos 6 meses: 60,9% das CJ com teste positivo vs. 43,2% com teste negativo relataram pelo menos um sintoma nos 6 meses após o teste; 27,6% das CJ com teste positivo vs. 15,9% com teste negativo relataram 3 ou mais sintomas. Os sintomas comuns aos 6 meses foram cansaço e falta de ar entre as CJ, tanto com teste positivo como com teste negativo. No entanto, a prevalência de ambos foi muito mais elevada nas CJ com teste positivo (38,4% e 22,8%, respetivamente) quando comparada com as CJ com teste negativo (26,7% e 10,9%, respetivamente). 24,5% das CJ com teste positivo vs. 17,8% com teste negativo cumpriram a definição do estudo de Delphi para síndrome pós-COVID-19. Os resultados de saúde mental, bem-estar, cansaço e qualidade de vida relacionada com a saúde foram semelhantes entre as CJ com teste positivo e com teste negativo 6 meses após o teste. Do mesmo modo, a sintomatologia foi semelhante entre CJ vacinadas contra a COVID-19 e não vacinadas contra a COVID-19, com teste positivo e com teste negativo.

Conclusões Seis meses após o teste PCR, as CJ que testaram positivo para a SARS-CoV-2 apresentaram sintomas similares aos das CJ que testaram negativo, mas as CJ com teste positivo apresentaram uma maior prevalência dos sintomas. A saúde mental, o bem-estar, a fadiga e a qualidade de vida relacionada com a saúde foram semelhantes entre as CJ com teste positivo e com teste negativo e os sintomas aos 6 meses foram semelhantes entre os vacinados e os não vacinados contra a COVID-19.

Número de registo do ensaio ISRCTN 34804192.

INTRODUCTION

Research on the long-term physical and mental health of SARS-CoV-2 infection in children and young people (CYP), who have also suffered from the indirect effects of the pandemic, including school closures, education disruption and social isolation, is key.¹

Our systematic review on persistent symptoms following SARS-CoV-2 in CYP found only 8 studies with an appropriate control group and 15 with an adequate follow-up period, mostly less than 4 months.² Published reports on the natural history of long COVID and persistence of both

Key messages

What is the key question?

- Few studies of long COVID in children and young people include a suitable comparison group.
- To our knowledge, no study has described self-reported overall health of children and young people 6 months after confirmed SARS-CoV-2 infection.
- No study has described post-COVID-19 symptoms in children and young people by vaccination status after proven SARS-CoV-2 infection.

What is the bottom line?

- Six-months post-PCR testing, adolescents who tested positive for SARS-CoV-2 had similar symptoms to those who tested negative, but test-positives had a higher prevalence of symptoms.
- Applying a Delphi-derived research definition of long COVID, 24.5% of test-positive and 17.8% of test-negative children and young people would be classified as having long COVID at 6 months.
- Physical, mental health, fatigue and health-related quality of life were similar among COVID-19-vaccinated and COVID-19-unvaccinated test-positive and test-negative children and young people.

Why read on?

- Six months post-test, there was little difference in mental health between test-positive and test-negative adolescents, suggesting the impact on mental health of SARS-CoV-2 infection is small.
- A symptom-based definition of 'long COVID' may not be ideal, and more detailed phenotyping looking for changes in biomarkers, immunotype and imaging is needed.
- Data from this subsample suggest that a COVID-19 vaccination policy based on reducing long-term symptoms in adolescents might not be efficacious.

physical and mental symptoms over time vary widely.^{3–9}

The effect of COVID-19 vaccination on persistent symptoms in CYP is not known. In the UK, vaccination was recommended in August 2021 for healthy adolescents aged 16–17 years old and September 2021 for those 12–15 years old.

By January 2022, 52.5% of adolescents aged 12–15 years old and 69.7% of those 16–17 years old in state-funded schools in England had received at least one dose of a COVID-19 vaccine, while 5.8% and 46.0%, respectively, received two doses.¹⁰

COVID-19 vaccination may reduce the risk of long COVID in adults who are subsequently infected with SARS-CoV-2.¹¹ Furthermore, for pre-existing long COVID in adults, vaccination was associated with a 12.8% decrease in self-reported prevalence of long COVID; a second dose was associated with an 8.8% decrease.¹²

We describe the physical and mental health of adolescents aged 11–17 years old, 6 months after PCR testing for SARS-CoV-2 infection in those who tested positive and tested negative and explore variation by COVID-19 vaccination status using data from the CLoCk Study,¹³ the largest, prospective, matched cohort study of test-positive and test-negative CYP.

METHODS

The CLoCk Study¹³ is a national cohort study of SARS-CoV-2 PCR-positive ('exposed') CYP aged 11–17 years, matched at study invitation, by month of test, age, sex and geographical area to SARS-CoV-2 test-negative ('unexposed') CYP using the national SARS-CoV-2 testing dataset held by the UK Health Security Agency (UKHSA). UKHSA received results of all SARS-CoV-2 PCR tests in England irrespective of reason (school attendance, contact of positive case, symptomatic). Only UK National Health Service number, name, age, sex and postcode were recorded. UKHSA can access the electronic Patient Demographic Service allowing us to approach CYP by post for them to consent online and undertake our questionnaire. The CLoCk Study involves follow-up for 2 years after a SARS-CoV-2 PCR test taken September 2020–March 2021. Depending on month of test, for some participants this is at 3, 6, 12 and 24 months post-test; for others 6, 12 and 24 months post-test; and for some 12 and 24 months post-test. This paper reports on all 6-month data post-test. Approximately 25% of these participants had reported follow-up data at 3 months post-test (see the Results section for details).

Measures

The questionnaire included demographics, elements of the International Severe Acute Respiratory and emerging Infection Consortium questionnaire,^{14–21} symptoms, the EQ-Visual Analogue Scale¹⁵ and EQ-5D-Y16 scale, Strengths and Difficulties Question-

naire (SDQ),¹⁷ Short Warwick-Edinburgh Mental Wellbeing Scale (SWEMWBS)¹⁸ and Chalder Fatigue Scale¹⁹ (online supplemental text 1). Those who consented completed the online questionnaire describing their health at the time of PCR testing (baseline) and 6 months post-test. Hence, baseline data relating to health at PCR testing were collected retrospectively; data 6 months later were collected prospectively.

CYP who were originally PCR negative but received a positive SARS-CoV-2 test by 6 months were excluded (determined by PCR test results held by UKHSA and self-report). Similarly, those who tested positive originally and were reinfected were also excluded. In addition, both test-positive and test-negative CYP were excluded if they responded to the 6-month questionnaire more than 34 weeks after their baseline PCR test.

Statistical methods

The representativeness of our study population was assessed by comparing their demographics (sex, age, region of residence and Index of Multiple Deprivation (IMD)) with those of the target population (all invited participants). Baseline characteristics of study participants, symptoms reported at PCR testing and symptoms reported 6 months post-test were further assessed according to SARS-CoV-2 status. As the prevalence of long COVID might vary by age,^{5–20} we also stratified analyses into two age groups, reflecting key educational stages (11–14 and 15–17 years).²¹

We operationalised our Delphi research definition of long COVID²² as having at least 1 of 21 symptoms and experiencing more than minimal problems on any one of the five EQ-5D-Y questions²³ (see footnote of online supplemental table 4). The Delphi definition requires laboratory confirmation of SARS-CoV-2 infection but of course that was not required when assessing how many test-negative CYP would also have met this definition. Participants' characteristics at baseline and 6 months post-test were stratified by SARS-CoV-2 test status and then further stratified by their long COVID status. Similarly, we produced tables stratified by SARS-CoV-2 infection and COVID-19 vaccination status. There were missing data only for information on vaccination (an optional question at the time of questionnaire completion), where 20 (15 PCR-negative and 5 PCR-positive) CYP did not answer. These CYP were omitted from tables stratifying by vaccination status.

To assess the effect of potential response bias, we reweighted all symptom frequencies according to the age, sex, region, IMD and

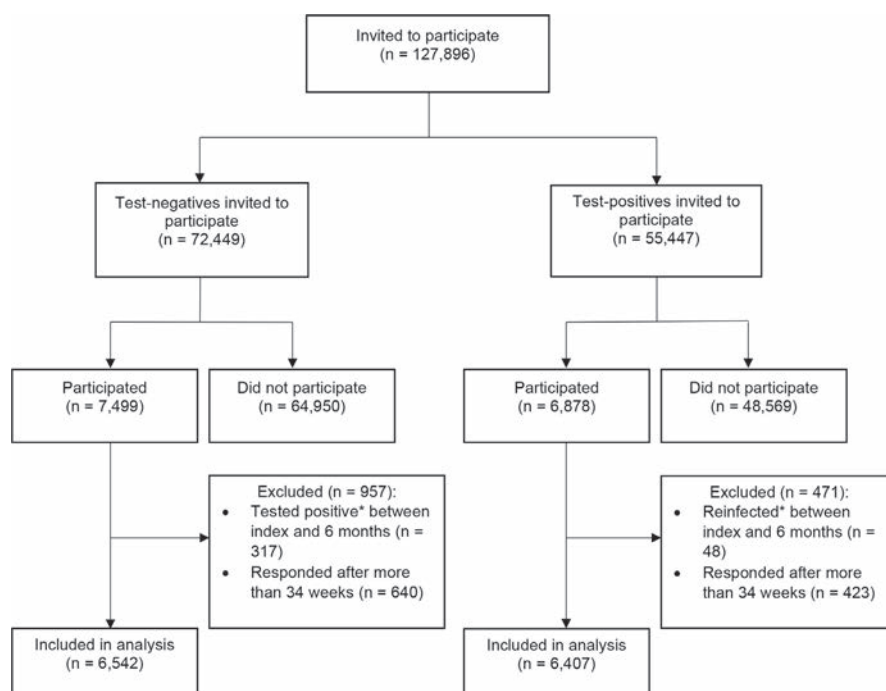


Figure 1 Participant flow. *Determined by PCR test results held by the UK Health Security Agency and self-report of whether (or not) the participant ever had a positive COVID-19 test.

SARS-CoV-2 status of the respondents so that analyses align with the characteristics of the target population.

This is a descriptive study and, in line with guidance, significance tests were avoided.²⁴ Therefore, our study does not assess causality nor report measures of association, and instead aims to describe distributions with the purpose of identifying areas for future formal investigation. This study is registered with the ISRCTN registry (ISRCTN 34804192).

RESULTS

A total of 14 377 participants completed a follow-up questionnaire 6 months after their SARS-CoV-2 PCR test between September 2020 and March 2021 (figure 1).¹³ Of these, 317 of 7499 CYP who were originally PCR negative received a positive SARS-CoV-2 test by 6 months and were excluded. Similarly, 48 of 6878 who tested positive originally were reinfected and excluded. An additional 1063 CYP (423 test positive and 640 test negative) were excluded because they responded to the 6-month questionnaire more than 34 weeks after their PCR test. The final study sample comprised 12 949 CYP (6407 tested positive, 6542 tested negative) and included 576 PCR-positive and 695 PCR-negative CYP who self-reported receiving a COVID-19 vaccine by their 6-month questionnaire. Although the study recruited non-hospitalised CYP at time of testing, 104 PCR-positive CYP did subsequently attend hospital appointments in relation to their COVID-19 infection of whom 50 were hospitalised over-night. A total of 1658 test-positive and 1737 test-negative participants who completed the questionnaire at 6 months had also completed the questionnaire at 3 months (when they reported on their baseline symptoms).²¹

The 6-month follow-up questionnaire was returned at a median of 27.8 (IQR: 26.3–29.7) weeks after testing. Overall, 6542 of 72 449 (9.0%) test-negative and 6407 of 55 447 (11.6%) test-positive CYP completing the 6-month questionnaire formed part of the analytical sample (see online supplemental table 1). Compared with the target population, both test-positive and test-negative respondents were more likely to be female and older teenagers (table 1). Study participants were also more likely to be from the East Midlands and the South West and less likely to be from London or the North West; they were also more likely to be from the least deprived areas. Test-negative and test-positive respondents in both the target population and analytical sample were broadly similar in terms of demographics, reflecting the matched cohort design.

At testing

At testing, test-positive CYP reported more symptoms than test-negative CYP (table 2). The most common symptoms among test-positive CYP were headaches, loss of smell and tiredness; among test-negative CYP they were sore throat, headaches and cough (table 2 and figure 2). The prevalence of symptoms varied by SARS-CoV-2 status (eg, headaches were reported by 29.0% of test-positive compared with 5.4% of test-negative CYP). The burden of symptoms was slightly higher at older ages (online supplemental table 2)

Six months post-testing

Six months post-testing, the most common symptoms in test-positive CYP were tiredness, shortness of breath, headaches, loss

Table 1 Demographics of target population and participants included in the 6-month sample

	Negative SARS-CoV-2 test		Positive SARS-CoV-2 test	
	Target population (N=72 449)	Study participants (N=6542)	Target population (N=55 447)	Study participants (N=6407)
Response rate		9.0%		11.6%
Sex				
Female	38 507 (53.2%)	4112 (62.9%)	29 443 (53.1%)	3992 (62.3%)
Male	33 942 (46.8%)	2430 (37.1%)	26 004 (46.9%)	2415 (37.7%)
Age (years)				
11–14	34 834 (48.1%)	2814 (43.0%)	26 757 (48.2%)	2759 (43.1%)
15–17	37 615 (51.9%)	3728 (57.0%)	28 690 (51.8%)	3648 (56.9%)
Ethnicity	Not recorded		Not recorded	
White		5083 (77.7%)		4919 (76.8%)
Asian, Asian British		856 (13.1%)		917 (14.3%)
Mixed		305 (4.7%)		265 (4.1%)
Black, African, Caribbean		172 (2.6%)		153 (2.4%)
Other		93 (1.4%)		112 (1.8%)
Prefer not to say		33 (0.5%)		41 (0.6%)
Region				
East Midlands	6232 (8.6%)	710 (10.9%)	4771 (8.6%)	643 (10.0%)
East of England	7273 (10.0%)	742 (11.3%)	5546 (10.0%)	649 (10.1%)
London	10 178 (14.0%)	824 (12.6%)	7950 (14.3%)	725 (11.3%)
North East England	4098 (5.7%)	379 (5.8%)	3079 (5.5%)	407 (6.4%)
North West England	13 590 (18.8%)	920 (14.1%)	10 363 (18.7%)	981 (15.3%)
South East England	8923 (12.3%)	890 (13.6%)	6816 (12.3%)	885 (13.8%)
South West England	4013 (5.5%)	489 (7.5%)	2934 (5.3%)	498 (7.8%)
West Midlands	9747 (13.5%)	877 (13.4%)	7386 (13.3%)	847 (13.2%)
Yorkshire and the Humber	8395 (11.6%)	711 (10.9%)	6602 (11.9%)	772 (12.1%)
IMD quintile*				
1 (most deprived)	21 584 (29.8%)	1286 (19.7%)	16 498 (29.8%)	1268 (19.8%)
2	14 737 (20.3%)	1175 (18.0%)	11 528 (20.8%)	1169 (18.3%)
3	12 546 (17.3%)	1220 (18.6%)	9589 (17.3%)	1120 (17.5%)
4	12 062 (16.6%)	1370 (20.9%)	9112 (16.4%)	1340 (20.9%)
5 (least deprived)	11 520 (15.9%)	1491 (22.8%)	8720 (15.7%)	1510 (23.6%)

*The IMD was calculated from the CYP's small local area level-based geographical hierarchy (lower super output area) at the time of the questionnaire and used as a proxy for socioeconomic status. We report IMD quintiles from most (quintile 1) to least (quintile 5) deprived. CYP, children and young people; IMD, Index of Multiple Deprivation.

of smell and dizziness in that order (table 2 and figure 2); all other symptoms affected less than 10% of test-positive CYP. The most common symptoms in test-negative CYP were tiredness, headaches and shortness of breath in that order; all other symptoms affected less than 10% of test-negative CYP. The prevalence of individual symptoms was higher in the test-positive CYP (table 2) and in the older age group (online supplemental table 3). Notably, 6 months post-test, despite the higher prevalence of symptoms in test-positive CYP compared with test-negative CYP, self-rated health was similar in both groups, overall and when stratified by age (online supplemental table 3).

Six months post-test, mental health and well-being were similar between test-positive and test-negative CYP. Among those aged 11–14 years old, the SDQ (total difficulties) median was 9 (IQR 5–14) for test-positive and 10 (IQR 6–15) for test-negative CYP (higher SDQ scores indicate more problems). Among those aged 15–17 years old, the SDQ median was 11 (IQR 7–16) for test-positive

and 12 (IQR 7–17) for test-negative CYP. The distribution of SWEMWBS scores (higher scores indicate better mental well-being) was similar between the test-positive (mean=21.7; SD 4.3) and the test-negative CYP (mean=21.4; SD 4.3). Mean fatigue scores (higher scores indicate more severe fatigue) were also similar between the test-positive (13.4; SD 5.1) and test-negative CYP (13.0; SD 5.1). EQ-5D-Y scores, representing health-related quality of life, showed that test-positive and test-negative CYP were equally likely to report problems with mobility, self-care, doing usual activities, pain/discomfort and feeling worried/sad, for example, 45.5% of test-positive CYP aged 15–17 years old, and 46.5% of test-negative CYP felt worried, sad or unhappy, as indicated on a single item of the EQ-5D-Y (figure 3).

Six months post-test, 24.5% of test-positive and 17.8% of test-negative CYP met our Delphi research definition of long COVID²² (online supplemental table 4). Regardless of SARS-CoV-2 status, those meeting the research definition of long COVID at 6 months

Table 2 Reported symptoms, and self-rated physical and mental health*, by SARS-CoV-2 status, at time of testing and 6 months post-test

	At time of testing		6 months post-test	
	Positive SARS-CoV-2 (n=6407)	Negative SARS-CoV-2 (n=6542)	Positive SARS-CoV-2 (n=6407)	Negative SARS-CoV-2 (n=6542)
No reported symptoms	3736 (58.3%)	5921 (90.5%)	2507 (39.1%)	3713 (56.8%)
1 symptom	239 (3.7%)	77 (1.2%)	1355 (21.2%)	1228 (18.8%)
2 symptoms	262 (4.1%)	94 (1.4%)	779 (12.2%)	563 (8.6%)
3 symptoms	297 (4.6%)	98 (1.5%)	569 (8.9%)	318 (4.9%)
4 symptoms	306 (4.8%)	83 (1.3%)	393 (6.1%)	216 (3.3%)
≥5 symptoms	1567 (24.5%)	269 (4.1%)	804 (12.6%)	504 (7.7%)
Specific symptoms				
Fever	1269 (19.8%)	279 (4.3%)	82 (1.3%)	96 (1.5%)
Chills	1002 (15.6%)	173 (2.6%)	479 (7.5%)	387 (5.9%)
Persistent cough	969 (15.1%)	310 (4.7%)	215 (3.4%)	209 (3.2%)
Tiredness	1607 (25.1%)	233 (3.6%)	2458 (38.4%)	1747 (26.7%)
Shortness of breath	759 (11.9%)	112 (1.7%)	1462 (22.8%)	710 (10.9%)
Loss of smell	1726 (26.9%)	117 (1.8%)	903 (14.1%)	90 (1.4%)
Unusually hoarse voice	299 (4.7%)	77 (1.2%)	98 (1.5%)	95 (1.5%)
Unusual chest pain	580 (9.1%)	116 (1.8%)	419 (6.5%)	234 (3.6%)
Unusual abdominal pain	299 (4.7%)	76 (1.2%)	288 (4.5%)	226 (3.5%)
Diarrhoea	299 (4.7%)	85 (1.3%)	181 (2.8%)	157 (2.4%)
Headaches	1858 (29.0%)	353 (5.4%)	1171 (18.3%)	825 (12.6%)
Confusion, disorientation or drowsiness	476 (7.4%)	53 (0.8%)	345 (5.4%)	218 (3.3%)
Unusual eye soreness	393 (6.1%)	54 (0.8%)	356 (5.6%)	260 (4.0%)
Skipping meals	782 (12.2%)	111 (1.7%)	609 (9.5%)	448 (6.9%)
Dizziness or light-headedness	1023 (16.0%)	180 (2.8%)	838 (13.1%)	535 (8.2%)
Sore throat	1418 (22.1%)	397 (6.1%)	414 (6.5%)	406 (6.2%)
Unusual strong muscle pains	670 (10.5%)	69 (1.1%)	286 (4.5%)	163 (2.5%)
Earache or ringing in ears	304 (4.7%)	66 (1.0%)	407 (6.4%)	284 (4.3%)
Raised welts on skin or swelling	71 (1.1%)	21 (0.3%)	73 (1.1%)	47 (0.7%)
Red/purple sores/blisters on feet	50 (0.8%)	14 (0.2%)	66 (1.0%)	58 (0.9%)
Other	209 (3.3%)	35 (0.5%)	488 (7.6%)	384 (5.9%)
Previous physical health*				
Very poor or poor	107 (1.7%)	148 (2.3%)		
Okay	1212 (18.9%)	1428 (21.8%)		
Good or very good	5088 (79.4%)	4966 (75.9%)		
Previous mental health*				
Very poor or poor	516 (8.1%)	667 (10.2%)		
Okay	1790 (27.9%)	1968 (30.1%)		
Good or very good	4101 (64.0%)	3907 (59.7%)		
Self-rated health†	90 (85–100)	90 (80–100)	90 (80–95)	90 (80–100)

Data are n (%).

*Participants were asked 'How was your physical/mental health in general before your COVID-19 test?' in two separate questions using a five-category Likert scale; we recoded these variables into three categories (very poor and poor, okay, and good and very good); questions were not asked in relation to 6 months post-test.

†Reported as median (IQR), measured by a Visual Analogue Scale (VAS) (EQ-5D VAS score), which records responses to the question 'Please look at the scale and select the number for your health BEFORE your COVID-19 test and your health TODAY'. Participants were told that '100% means the best health you can think of; 0% means the worst health you can think of'.

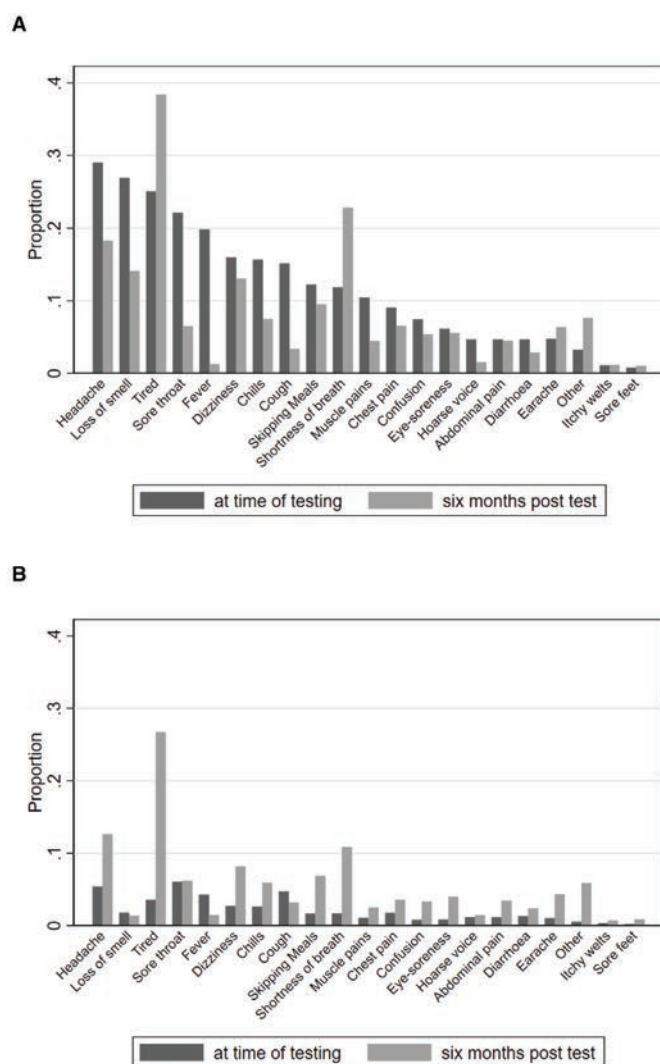


Figure 2 Proportion of participants experiencing symptoms at time of testing and 6 months post-testing by SARS-CoV-2 status: (A) test-positive children and young people (CYP) and (B) test-negative CYP.

also reported worse mental health, well-being and fatigue (online supplemental table 5).

Between testing and 6 months post-test, 10.7% of test-negative and 9.0% of test-positive CYP received a COVID-19 vaccine (online supplemental table 6). When assessed by SARS-CoV-2 PCR test status at baseline, there was little difference between vaccinated and unvaccinated CYP in terms of symptoms, mental health or well-being at 6 months post-test (online supplemental table 7).

When we reweighted the percentage of reported symptoms at baseline and at 6 months post-test according to the age, sex, region, IMD and SARS-CoV-2 test status of the respondents, so that analyses align with the characteristics of the target population, broadly similar patterns were observed to those reported above (online supplemental table 8).

DISCUSSION

At time of testing for SARS-CoV-2 infection, test-positive CYP reported more symptoms than test-negative CYP. Six months post-testing, the overall prevalence of symptoms had increased in both groups and the prevalence of symptoms remained higher in test-positive compared with test-negative CYP. As in our previous analysis at 3 months post-test,²¹ prevalence of tiredness and shortness of breath increased at 6 months post-test compared with baseline in both test-positive and test-negative CYP. It is these two large increases which underlie the overall increase in symptom prevalence in both groups. This may be partly due to self-selection by participants with symptoms to report. Study participants were more likely to be female, older, from certain geographical areas and from less deprived areas.

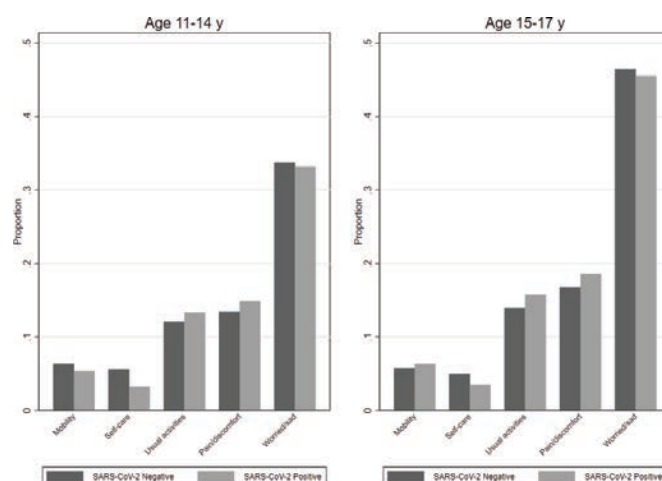


Figure 3 Proportion of participants reporting experiencing some or a lot of problems 6 months post-test by SARS-CoV-2 status, by age. *Assessed using the five items from the EQ-5D-Y scale, each of which has a three-level response (no problems, some problems, a lot of problems). The graph shows the proportion who experiences some/a lot of problems with mobility, self-care, doing usual activities, having pain/discomfort, or feeling a bit/very worried/sad.

Employing our Delphi consensus definition of long COVID in CYP,²² those without long COVID are more likely to be male, younger, and have good/very good physical and mental health before PCR testing (online supplemental table 4).

With respect to mental health, well-being and fatigue 6 months post-test, there was little difference in scores between test-positive and test-negative CYP. Moreover, the scores were very similar to those we described at 3-month follow-up.²¹ For example, at both 3 and 6 months post-test, median SDQ was 9–12 depending on age.

It might appear incongruent that 6 months post-test, while test-positive CYP had a higher prevalence of symptoms than test-negative CYP, their mental health, self-rated health, well-being and fatigue levels were similar. These observations suggest that by 6 months post-test, while test-positive CYP do experience more symptoms than test-negative CYP, these symptoms are mostly mild with little effect on overall well-being.

Acknowledging only 10% of CYP were vaccinated by 6 months post-test, we found little difference in symptoms, mental health or well-being at 6 months in vaccinated and unvaccinated PCR-positive and PCR-negative CYP. Indeed, EQ-5D-Y scores were somewhat worse and self-rated health lower, for the vaccinated group, which could represent self-selection of more severely affected CYP undergoing vaccination or self-selection of respondents.

The very few studies with follow-up of CYP for at least 6 months after SARS-CoV-2 infection^{4,6,7} show conflicting findings. However, all findings, including ours, need to be considered within the context of bias (selection and recall), low response rates and recognising that a temporal association with infection does not prove causality as indirect effects of the pandemic need to be considered.²⁵ Therefore, our findings are important because we have a test-negative group of CYP who have lived through the 'long pandemic' and who never tested positive for SARS-CoV-2 before or during the study period, although we acknowledge that (re)infections may have gone undetected. However, PCR and lateral flow tests were widely and freely available in the UK before and during the 6 months post-test period (April–September 2021). Hence, our data provide a unique perspective on long COVID in CYP.

Our study has limitations.²¹ First, the questionnaire response rate was low (9.0% (test-negative CYP); 11.6% (test-positive CYP)). However, this is similar to the Office for National Statistics random household survey (response rate 12% October 2021, Daniel Ayoubkhani: personal communication). Second,

the study design may risk selection biases of those with internet access; symptoms to report (perhaps explaining why relative frequencies of many symptoms were higher 6 months post-test compared with baseline); recall bias for symptoms at time of testing; returning to school from March 2021, following national lockdown from January 2021, with exposure to other infections. Furthermore, some symptoms might have predated SARS-CoV-2 infection. Participants did not report on symptom severity. Third, although the number of symptoms is a proxy of illness severity, a single severe symptom might be more disabling than several mild symptoms. EQ-5D-Y served as a severity indicator because it assesses the effect on daily living. Fourth, it is possible that some participants might have been misdiagnosed as SARS-CoV-2 negative and vice-versa. False negatives can arise from PCR timing, swab technique and assay sensitivity but false-positive PCR results are rare. Fifth, we could not recruit or match on ethnicity, medical history or testing location but subsequent self-reported ethnicity was very similar in both test groups and geographical address served as a proxy for socioeconomic status. We used established scales to measure mental health, well-being and fatigue but acknowledge the limitations of self-reporting and floor and ceiling effects.

All self-reported symptoms are subjective. Researchers want to ask as much as possible to allow analysis of as many research questions as possible. In our pilot, the researchers' initial draft questionnaire took over an hour to complete and teenagers said they would be willing to spend 20 minutes maximum completing the survey, despite a financial reward. This compromise means our wide-ranging and unique data have limitations in terms of information available

CONCLUSIONS

Tiredness and shortness of breath were two dominant symptoms 6 months after SARS-CoV-2 PCR testing, irrespective of test result. Secondly, 27.6% of test-positive and 15.9% of test-negative CYP had three or more physical symptoms 6 months post-test, which was similar to the 30.3% and 16.2%, respectively, we reported at 3 months post-test.²¹ Thirdly, at 6 months post-test, there was little difference in well-being and mental health between test-positive and test-negative CYP. Fourth, 24.5% of test-positive CYP met our Delphi definition of long COVID²² at 6 months compared with 17.8% of test-negative CYP. Finally, the profile of symptoms, well-being and mental health in test-positive and test-negative CYP by COVID-19 vaccination status was similar.

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Contributors TS conceived the idea for the study, submitted the successful grant application and drafted the manuscript. SPP designed and conducted the statistical analyses for the manuscript, accessed and verified the data and drafted the manuscript. SPP acts as guarantor for the manuscript. RS contributed to the design of the study, submitted the ethics and R&D applications and drafted the manuscript. MDN conducted the statistical analysis for the manuscript, accessed and verified the data and drafted the manuscript. NKR assisted with the statistical analysis for the manuscript, accessed the data and reviewed the manuscript. KM adapted the questionnaire for the online SNAP survey platform. RS accessed and verified the data, designed the participant sampling and data flow. TF contributed to the design of the study and reviewed the manuscript. IH contributed to the design of the study and reviewed the manuscript. SNL developed the study methodology, operationalised the regulatory and recruitment ideas for the study and revised the manuscript. EYC assisted with the references for the literature review and contributed to the manuscript. LF-S assisted with the drafting, formatting of the manuscript and references. ED conducted the PPI meetings, contributed to and reviewed the manuscript. All members of the CLoCk Consortium made contributions to the conception or design of the work and were involved in the funding application and this manuscript.

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Competing interests TS is Chair of the Health Research Authority and therefore recused himself from the Research Ethics Application. Trudie Chalder is a member of the National Institute for Health and Care Excellence committee for long COVID. She has written self-help books on chronic fatigue and has done workshops on chronic fatigue and post-infectious syndromes.

Patient consent for publication Not required.

Ethics approval This study involves human participants and ethical approval was provided by the Yorkshire and the Humber- South Yorkshire Research Ethics Committee (REC reference: 21/YH/0060; IRAS project ID:293495). Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are not publicly available. All requests for data will be reviewed by the Children & young people with Long Covid (CLoCk) Study team, to verify whether the request is subject to any intellectual property or confidentiality obligations. Requests for access to the participant-level data from this study can be submitted via email to: CLoCk@phe.gov.uk with detailed proposals for approval. A signed data access agreement with the CLoCk team is required before accessing shared data. Code is not made available as we have not used custom code or algorithms central to our conclusions.

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Sistemas de alerta precoce pediátrico: não existe uma resposta simples para uma questão complexa

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RESUMO

Os sistemas de alerta precoce pediátricos (SAPP) para reduzir a mortalidade hospitalar têm sido um esforço louvável.

A avaliação do seu impacto raramente examinou a validade interna dos componentes dos SAPP na obtenção dos resultados desejados. Destacamos as suposições feitas em relação ao modo de ação dos SAPP e, à medida que os SAPP se vão tornando mais comuns, esta tese questiona se, na realidade, compreendemos bem a sua função, processo e resultado.

BACKGROUND

In adult clinical practice, the incidence of preventable inpatient mortality is significant (with potentially over 22 000 preventable deaths annually in the 'USA) and has precipitated the development of a variety of interventions to standardise the processes for recognition and response to evolving inpatient deterioration. These have been delivered by the use of early warning systems (EWS) to aid recognition and response to patient deterioration² which have included:

1. The development of track and trigger tools³ (numerical values assigned to commonly measured physiological and observation values which produce a composite score that correlates to an escalating response process dependant on the score)
2. Rapid response teams (RRTs)⁴ (experienced staff assigned to respond to patients who trigger criteria predictive of impending need for intensive care) and
3. Critical care inreach and outreach⁵ (deploying specialist critical care staff to non-intensive care settings to prevent admission and outreach to prevent readmission to critical care).

Determining effectiveness is challenging and data on system-level improvement in mortality are sparse. The concept of EWS in the UK was discussed as early as 1997⁶ and the Royal College of Physicians recommended their use in 2007.⁷ Since this point, publicly available data have shown inpatient hospital mortality has actually risen from 275 000 in 2014⁸ to 293 000⁹ in 2019 (uncontrolled for population growth or number of hospitals). The interventions (1–3) above have different impacts and the relationship between a specific intervention and an outcome is not always clear. For example an RRT is dependent on processes which enable not only initial recognition of deterioration, but require an institution to have experienced personnel available to make time-critical decisions on patients and have the capacity to provide appropriate resources if care needs to be escalated. It has been suggested that adult RRTs were implemented to address a problem without fully understanding the context of the problem and the system in which these problems exist¹⁰ but the face validity that RRT should work and the impetus to improve

patient safety was so strong that limited evaluation of its mechanism of action took place. A subsequent systematic review has demonstrated a variety of non-patient-based factors to also be important,¹¹ such as leadership and punitive hierarchies. This is similar to the introduction of pulse oximetry, which had minimal level 1 evidence supporting its introduction. The ease of measuring oxygen levels is so great it would now be unethical to undertake a study randomising patients to a control group.¹² Acknowledging these experiences in adult practice by examining the link between intervention and outcome with a paediatric lens, we will explore what we know about the effectiveness of EWS for use in children (paediatric early warning systems, PEWS) and what this means for the development of outcome measures.

CHALLENGES WITH DETERMINING EFFECTIVENESS

The first published Paediatric Early Warning Score in the UK was in 2005 with multiple iterations published since and nearly all hospitals in England now using some form of a score.¹³ In a recent systematic review, our group examined 30 studies to determine the effectiveness of paediatric track and trigger tools (PTTT).¹⁴ These studies were predominantly before and after studies using a variety of outcomes. These can be categorised into discrete outcome measures which have been grouped by frequency in table 1. There is great variation among studies in the precise definition of a code blue, cardiac arrest, respiratory arrest, unplanned admission to paediatric intensive care unit (PICU), and the criteria for PICU admission or high-dependency admission, making comparisons of PTTTs difficult. Denominator variation for mortality and cardiac arrest figures, different types of controls used in studies or indeed no control groups, as well as study design variability, all compound that challenge. In particular, denominators are challenging to calculate as they are often recorded as patient bed days, rather than raw patient numbers which can suffer from poor data recording (eg, over weekends).

It is also important to note that most studies were conducted in specialist and tertiary centres where specialist intensive care advice is available on-site. These outcomes are therefore not representative of what is measured, or can be measured, in hospitals without direct access to intensive care. In these centres, where most hospitalised children in the UK are admitted, different decisions may be made about escalation, because of the lack of immediate access to both a PICU bed and critical care trained clinicians. Furthermore, children may deteriorate in one hospital without intensive care facilities but die in another which has them. It may then not be clear which interventions in either hospital were most impactful, or lacking, making causation and the role of PTTT difficult to ascertain. Therefore, if

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Table 1 Range of outcome measures in a review of track and trigger systems¹⁴

Outcome measure	Number of studies
Cardiac arrest or code blue call	6
Urgent or unplanned PICU admission	17
Composite of death or unplanned PICU admission	15
Emergency medical intervention	2
Unplanned high dependency unit	2
Other	2

PTTT Scores are being used in non-specialist hospitals, it cannot be assumed the outcomes from their use will be the same as in tertiary hospitals. This also applies to their use in emergency departments, and prehospital settings, by paramedical staff and in primary care. PTTTs provide a mechanism to proactively highlight the need for review of a child who is becoming clinically unstable. In prehospital and emergency department locations a high PTTT Score may be representative of a child's initial acuity rather than evidence of deterioration. The relationship between a high PTTT Score and a specific outcome is then less certain. Furthermore, the pretest probability for serious disease (which may result in deterioration) is much lower in emergency departments and prehospital settings therefore altering a PTTT's specificity and sensitivity. It is perhaps for these reasons a paucity of evidence exists on the performance of PTTT Scores in these environments.^{15 16}

CHALLENGES WITH DELIVERING EFFECTIVE SYSTEMS

The use of PTTTs with low specificity and low positive predictive values¹⁷ may result in alarm fatigue, short cuts to bypass the system and disengagement with the system overall.¹⁸ Adjustment of 'normal' vital sign triggering thresholds may be necessary for some high-risk groups of children (eg, children with congenital heart conditions), but if done by inexperienced staff or without evidence-based data, may reduce triggering of a PTTT and consequent failure to detect deterioration. Conversely, unnecessary critical care admission reduces capacity in an already strained system, is resource-intensive and may redirect experienced staff to clinical areas where they are not needed.

PEWS are complex due to the requirement for age-specific thresholds and difficulties ascertaining their effectiveness due to the lower mortality in children than in adults.¹⁹ All-cause mortality in children and young people continues to decline over time²⁰ and a decade ago, Joffe and colleagues²¹ demonstrated that improvements in mortality previously attributed to patient safety systems, such as RRT, were also occurring in hospitals without such interventions. Childhood avoidable mortality in the UK (causes of death such as from infection or treatable conditions such as appendicitis) has fallen from 2726 in 2001, to 1902 in 2010 and then to 1473 in 2019.²² This trend infers that while PEWS have a role to play there are other systematic factors impacting mortality rates. Where mortality has been used as an outcome measure in evaluating the effectiveness of PTTT (and for comparison in adults there were 293 000 inpatient deaths in 2019) the studies are mixed,²³ which has led to debate about their utility.¹⁹ A cluster randomised control trial comparing 10 hospitals in which the bedside PEWS (a PTTT) was implemented, with 11 control hospitals where there was no PTTT, failed to demonstrate an impact on mortality.²⁴ During this study, that examined over 500 000 inpatient days in 150 000 children, there were fewer than two observed deaths per 1000 hospital discharges across both arms, and in approximately half of these deaths, 'do not attempt resuscitation' orders were in place. There has been one further randomised control trial published (comparing two different PTTT Scores) which concluded the results should be interpreted with caution given the low rate of clinical deterioration (only 22 unplanned transfers of care in 31 337 admissions to the recruiting paediatric hospitals).²⁵ Therefore, it is reasonable to conclude the use of mortality as the primary outcome measure in these studies of PTTTs effectiveness is not robust.²⁶

WHICH ARE THE MOST RELEVANT OUTCOMES?

While mortality is infrequent, it is catastrophic for both families and staff, so it is important we understand how these interventions may impact on the variety of processes that may lead to this tragic outcome. PEWS are a complex healthcare intervention,²⁷ and it is difficult to determine which components impact on the quality of clinical processes, and the mechanisms by which each part exerts its effects. National reports continue to highlight the need for quality improvement in recognising and responding to inpatient deterioration and therefore healthcare organisations and regulators need to be able to assess which components of PEWS are effective across a range of process and outcome measures. Due to the focus on mortality as the end point in the deterioration pathway, some safety mechanisms that work well before deterioration and therefore avoid intensive care, may have been missed. There is a paucity of early or intermediate outcomes. Where they have been developed, they are rarely used as primary outcome measures.^{28,29} It is likely directing all improvement efforts to solely preventing mortality (as has legitimately occurred in adult practice) may impact on a host of balancing measures which affect productivity and resources. Our recent evidence-based, theoretically informed, Paediatric early warning system - Utilisation and Mortality Avoidance. improvement programme (PUMA Programme) was developed and implemented in two general hospitals (no onsite PICU) and two tertiary hospitals (with onsite PICU) in the UK.³⁰ We developed a composite metric (adverse events) as a primary quantitative outcome representing the number of children monthly that experienced one of the following: mortality, cardiac arrest, respiratory arrest, unplanned admission to PICU or unplanned admission to a higher dependency unit. Despite implementation challenges, all made contextually appropriate system changes with a decline in the adverse event rate at three sites. At the site in which system changes were organisationally adopted, this decline was significant. The variable impact on adverse rates highlights the dynamic qualities of PEWS. As an example, the introduction of an electronic EWS at one of the sites strengthened medical access to patient data but disrupted nursing work as there were insufficient computers available to allow nurses to enter vital signs, leading to a delay between monitoring and recording the PTTT Scores.

HOW MIGHT PEWS FUNCTION?

The lack of system-wide data demonstrating a specific impact of PEWS on mortality does not mean they are not effective for other outcomes, but that these outcomes have yet to be measured or realised. Furthermore, numerous different processes might contribute to an overall benefit, but a given individual intervention might not reach significance. These interventions may be relatively simple, from the production of minimum training standards for staff who will be involved in caring for patients on PEWS pathways, to complex electronic whiteboard systems which can highlight deterioration of patients, to command control centres remote from wards. Some interventions may also be embedded in processes which already occur, such as a morning handover. These may not previously have been regarded as interventions but will probably have been recognised as being beneficial by staff and institutions. Another example of an unrecognised intervention is that of situational awareness. This encompasses processes such as bringing staff together in huddles³¹ and identifying 'watcher' patients through shared communication processes.³² Watcher patients are those identified through nursing staffs' tacit knowledge; for example, the identification of a patient who appears well at present, but the nurse's experience dictates they are at risk of deterioration, even though the nurse cannot completely explain exactly why. Understanding whether, and more importantly how, these interventions take place needs a system assessment requiring more of a focused evaluation than a simple 'yes/no' questionnaire. A clinical area may claim they don't use watchers, but this may be what staff are doing; conversely both clinicians and operational managers may claim they have strong situational awareness, but in reality, might be dependent on traditional communication hierarchies. Finally, it is also important there are the right number of staff, with the right

Table 2 The core components of a paediatric early warning system: the PUMA standard

	Proposition	Conceptual requirements
Detection	Detection of deterioration depends on timely and appropriate monitoring of vital signs and relevant risk factors	At a minimum, this requires: ► Staff are aware of which vital signs need to be monitored ► Staff are aware of the minimum frequency of observations required for the children in their care ► Staff are aware of the need to review the frequency of observations for children in their care ► Staff are aware of additional clinical assessments required for children with prior risk factors ► Monitoring tasks are allocated to staff members with appropriate skills to conduct them ► Staff have access to appropriate equipment to accurately monitor vital signs, and conduct other clinical assessments ► Staff are aware of roles and responsibilities for monitoring ► Staff have time to conduct accurate timely and appropriate monitoring of vital signs, alongside other work commitments ► Staff concern is formally recognised as a valid indicator of deterioration ► Staff are supported to develop and use their intuition in detecting signs of deterioration ► Staff understand the value of family concerns in the detection of deterioration ► Families are involved with defining normal physiological parameters for their child ► Families receive guidance about what to do if they are concerned that their child's condition is deteriorating ► Staff keep families informed about developments in their child's care and treatment
	Detection of deterioration depends on timely and appropriate recording of signs of deterioration	At a minimum this requires: ► Staff are aware of the need to record vital signs, family concern and staff concern promptly and accurately ► Staff are aware of roles and responsibilities for recording vital signs, family concern and staff concern ► Staff have appropriate skills to accurately record vital signs, family concern and staff concern ► Staff have access to appropriate equipment to accurately record vital signs, family concern and staff concern ► There are an appropriate number of staff to carry out required tasks
	Detection of deterioration depends on timely and appropriate interpretation of signs of deterioration	At a minimum this requires: ► Staff are aware of prior factors that increase children's risk of deterioration (eg, premature birth) ► Staff are aware of roles and responsibilities for interpreting signs of deterioration ► Staff take into account vital signs, family concern and staff concern in assessing the condition of children in their care ► Teams have appropriate skills to discern patterns and trends of signs and symptoms ► Staff have the opportunity to learn how to interpret signs of deterioration from shadowing more senior staff ► Care is organised to enable staff to recognise patterns and trends for children ► Families are in a position to discern patterns of signs and symptoms in their child
	Proposition	Conceptual requirements
Planning	Planning depends on reviewing indicators of deterioration for each patient	At a minimum this requires: ► For each child, all indicators of deterioration are brought together and kept up to date ► There is a regular mechanism for reviewing the status of all children in the ward to identify those children who are a concern ► There is a regular mechanism for reviewing staffing levels and skills mix, workload, acuity and admissions
	Planning depends on staff being aware at ward level of the status of individual patients and the availability of skills and resources, and preparing an appropriate response	At a minimum this requires: ► There is a regular mechanism for communicating the review of all children, staffing levels and other resources to the rest of the team and senior managers ► There is a regular mechanism for planning appropriate response to deterioration ► Senior staff members are allocated responsibility for managing demand and resources ► Senior staff members are allocated responsibility for communicating response plans ► There is an action plan for children at risk of deterioration which is shared with families and staff caring for them
	Proposition	Conceptual requirements
Action	Action depends on clear escalation and response processes	At a minimum this requires: ► A trigger or prompt to act from detection or planning phases ► Clearly defined graded escalation and response procedures—agreed at organisational level ► Staff receive guidance about how to escalate and respond ► Staff understand their roles and responsibilities in the escalation procedure as activators and responders ► Staff are encouraged and supported in raising concerns ► Families are encouraged and supported in raising concerns ► Staff are able to communicate information across professional hierarchies using a structured approach to sharing information ► Clear structures to support action, including the use of a 'no false alarms' policy so staff are not deterred from escalating care
	Action depends on evaluation	At a minimum this requires: ► Escalation and response processes are reviewed to promote learning ► There is opportunity for staff to discuss differences of opinion in the need for escalation ► No blame is assigned to those who escalate

tools, to enable them to perform the right task, at the right time. The availability (or absence of) equipment to effectively monitor a patient (such as functional pulse oximeters and correct sized blood pressure cuffs, etc) clearly impacts on the ability to detect and plan for a child becoming unexpectedly unwell. Adequate staffing is an important safety factor in itself and demand for child health services outstrips capacity with workforce issues being 'a significant challenge to child health service delivery and improvement' according to the latest Royal College of Paediatrics and Child Health review of the medical and nursing workforce.³³

Interventions which aid parents', carers' and professionals' ability to raise concerns about imminent deterioration in a child, and processes to measure this, would also provide an organisation with knowledge of this important facet of care. Organisational cultures have a significant impact on outcomes³⁴ and actively demonstrating that patients, families and carers are involved in, and feel able to share concerns around, decision making is an important outcome in itself. Discrete outcomes such as mortality or ICU admission are easy to measure but other interventions, such as improving and maintaining situational awareness at a patient, ward and

organisational level are also likely to have a positive impact on deterioration. They may also improve negative hierarchical cultures (an often unexplored but significant influencer on care) and therefore are an important part of clinical practice. The absence of studies examining the link between these organisational and human factor characteristics and specific outcomes is something that needs to be addressed with further study. A scoping review of PEWS undertaken in 2021 reiterated the need to understand both the 'technical' nature of any score and the wider social, cultural and organisational context in which they are deployed.³⁵

Our PUMA programme assessment tool evaluates a system's ability to Detect, Plan and Act in response to the deteriorating child. It provides a detailed description of what needs to be in place for children's deterioration to be detected and acted on. This propositional model detailed in table 2 contains interventions, tasks and skill sets that are not always possible to link to specific patient outcomes but represent a positive safety culture in a particular ward environment. Constructs such as a no blame environment, empowerment, communication, situational awareness, psychological safety, clear leadership, closed loop feedback, teaching and so

Box 1 Outcomes used in all the paediatric early warning systems (PEWS) 'validation studies'

Death

1. Hospital-wide deaths per 100 discharges
2. Hospital-wide deaths per 1000 discharges
3. Ward deaths only per 1000 admissions
4. All-cause hospital-wide mortality rate
5. Deaths on paediatric intensive care unit (PICU)
6. PICU deaths for all ward transfers
7. PICU mortality rates among readmitted patients in 24 hours

Cardiac arrests/respiratory arrest

8. Near cardiopulmonary arrests
9. Cardiac arrest
10. Actual cardiopulmonary arrests
11. Unexpected cardiac arrests
12. Ward respiratory arrests per 1000 patient days
13. Preventable cardiac arrests

PICU/PHDU

14. Unplanned transfer to PICU ($\pm$ within 24 hours of admission)
15. Unplanned PICU transfers per 1000 patient days
16. Critical deterioration events (life-sustaining interventions administered within 12 hours of PICU admission)
17. Invasive ventilation given to emergency admissions to PICU postintervention
18. Early intubation
19. Postintervention rates of PICU admissions receiving mechanical ventilation
20. Unplanned transfer to Paediatric High Dependency Unit (PHDU) $\pm$ within 24 hours of admission)

Urgent consult/review assistance/urgent review

21. Code calls
22. Urgent calls to inhouse paediatrician
23. Urgent calls to respiratory therapist
24. Rapid response team (RRT) call
25. Outreach team calls
26. (Phone call advice/consults to PICU team)
27. Specific 'Intervention' with RRT—on ward

Composite measures

28. Combined cardiac and pulmonary arrests
29. Critical deterioration index (non-invasive or invasive ventilation and/or inotropic support within 12 hours after admission)
30. Critical deterioration index (non-invasive or invasive ventilation and/or inotropic support within 24 hours of admission)

on are persistently recognised as being of importance. Certainly there is evidence from our qualitative examination of these systems that PEWS aid staff in having a common language for communication about deterioration.³⁶ This might explain why PEWS have continued to spread^{13 37} despite equipoise on their utility and is a reason why national scores exist in Scotland and Ireland. The English National Health Service has started a schedule of activity to introduce a standardised inpatient PEWS chart.³⁸ This work is part of an overarching System-wide Paediatric Observation Tracking (SPOT) programme. The utilisation of standardised outcomes and end points, being developed as part of the programme, will hopefully avoid further heterogeneous results which will be difficult to interpret. An expert working group has taken a list of potential outcome measures derived from a previous systematic review¹⁴ (box 1) and refined it to create a panel which will be measured in real time, both nationally and regionally, as the inpatient implementation rolls out. Following feasibility and usability exercises undertaken in a small group of hospitals a prototype chart has been rolled out in a number of pilot sites. This prototype chart

has been developed via consensus opinion from multiple specialties with medical and nursing inputs. A community of practice has been created with weekly meetings examining enablers and barriers to effective de-implementation (all pilot sites already have a PEWS system in place and so this exercise is in changing rather than generating new practice). The pilot chart is continually being refined as a result of feedback from the pilot sites and a version 4.0 will be released in the late summer of 2022. The new version will undergo further real-world testing before a final version will be released later in 2022 for early adopter sites to implement. This programme of work has the support of National Health Service England (NHS England), The Royal College of Paediatrics and Child Health and the Royal College of Nursing with further information available via the Royal College of Paediatrics and Child Health (RCPCH) website.³⁹

CONCLUSION

Healthcare organisations, academic institutions and regulators recommending PEWS as an answer to the problem of inpatient deterioration without understanding all the mechanisms of their action will deliver research and implementation studies with equivocal findings. The rapid spread of PEWS over the last decade is testament to their positive face validity and undoubtedly they have contributed to an improved safety culture. Ultimately we have not yet identified the specific ingredients and mechanisms by which PEWS work as we don't have the outcomes by which to test different recipes. To improve outcomes for children in inpatient settings we must change the emphasis from rare outcomes (mortality) and examine and measure a wide range of interventions that may aid early detection of deterioration. This work has arisen from a study/project funded by the National Institute for Health Research, Health Services and Delivery Research Programme, funder reference: 12/178/17. The views expressed are those of the author(s) and not necessarily those of the National Institute for Health Research or the Department of Health and Social Care.

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Contributors All authors were co-investigators on the PUMA Study cited in the article. DR wrote the initial draft of the manuscript; with all authors contributing to subsequent revisions and confirming the final submitted manuscript.

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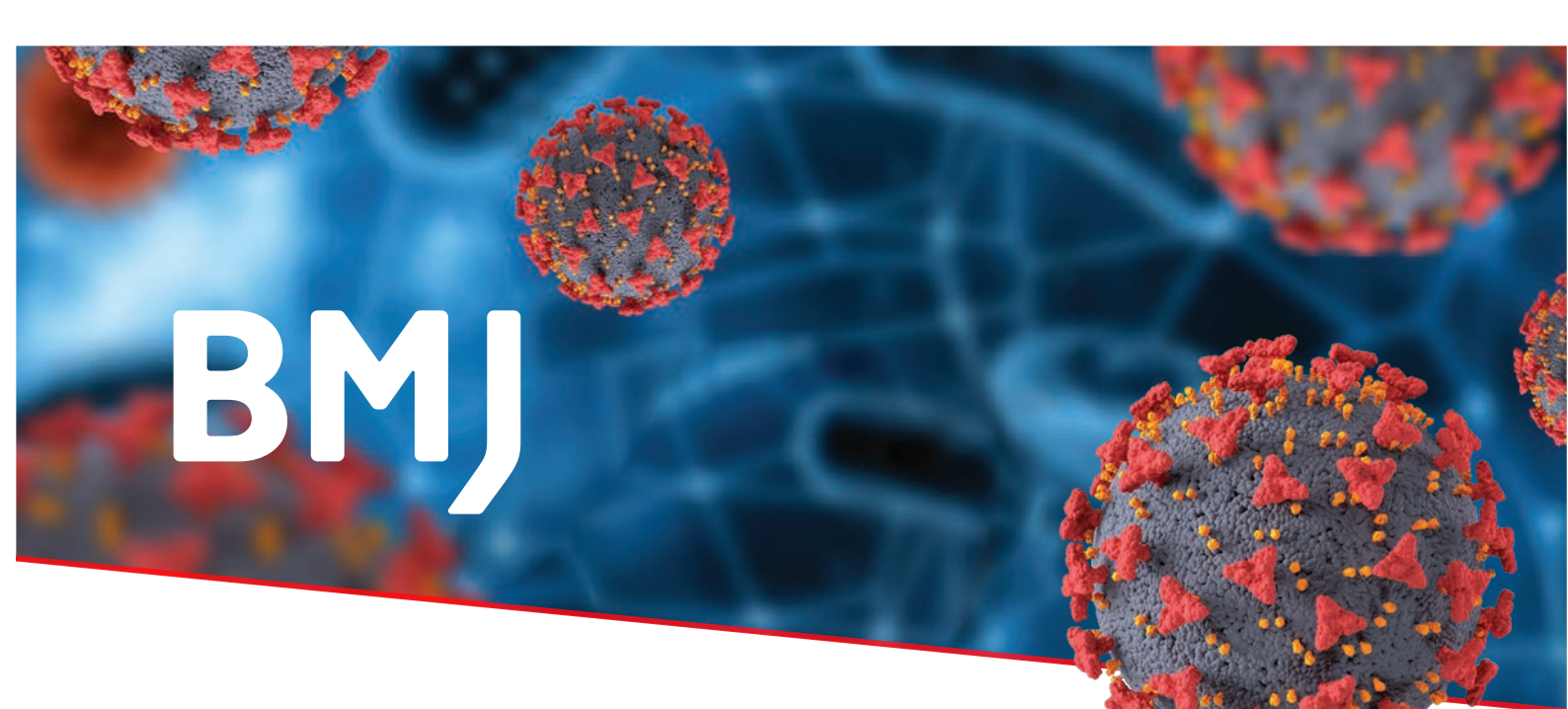
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Avaliação do tratamento formal do tabagismo e da interrupção do hábito de fumar em fumadores duais de cigarros combustíveis e cigarros eletrônicos

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RESUMO

Contexto A utilidade dos cigarros eletrônicos como auxiliares para deixar de fumar permanece pouco clara. Da mesma maneira, é pouco claro que o tratamento formal do tabagismo (farmacoterapia e/ou apoio comportamental) aumente a interrupção do consumo de tabaco nos indivíduos que usam tanto cigarros combustíveis quanto eletrônicos.

Métodos Realizamos um estudo longitudinal de adultos em ambulatório avaliados no nosso centro de cuidados médicos terciários (6/2018 – 6/2020). A utilização de cigarros eletrônicos, o estado tabágico e o tratamento formal do tabagismo (farmacoterapia de dissuasão e/ou apoio comportamental) foram avaliados em blocos de 6 meses (por exemplo, coorte 1 (C1)=6/2018 – 12/2018, C2=1/201 – 6/2019, e por aí em diante) ou utilizando o nosso registro de saúde eletrônico. Avaliámos a relação entre a utilização de cigarros eletrônicos (com ou sem tratamento formal do tabagismo) e prevalência pontual da interrupção do hábito de fumar aos 6 e 12 meses.

Resultados Foram incluídos no estudo 111 823 pacientes individuais. A prevalência da utilização dupla de cigarros combustíveis e eletrônicos aumentou significativamente durante o período do estudo (C1=0,8%; C2=1,1%; C3=1,8%; C4=2,3%; $p<0,001$).

A prevalência da interrupção do hábito de fumar aos 12 meses foi mais elevada entre os utilizadores de cigarros eletrônicos (20,8%) quando comparada com os não utilizadores (16,8%) [diferença de risco, 4,0% (IC 95%, 2,5% a 5,5%); risco relativo ajustado (aRR) 1,354 (IC 95%, 1,252 a 1,464, $p<0,0001$)]. Além disso, entre os utilizadores duais de cigarros combustíveis e eletrônicos, a prevalência da interrupção do hábito de fumar aos 12 meses era mais elevada entre os indivíduos que receberam tratamento de tabagismo (29,1%) quando comparados com os indivíduos que não receberam tratamento de tabagismo (19,6%) [diferença de risco, 9,5% (IC 95%, 4,6% a 14,4%); aRR 1,238 (IC 95%, 1,071 a 1,432, $p<0,004$)].

Interpretação Estes resultados sugerem que os utilizadores duais de cigarros combustíveis e eletrônicos beneficiam de um tratamento formal de tabagismo. Os médicos devem considerar a sugestão de tratamento formal de tabagismo a estes pacientes, embora sejam necessários mais estudos.

INTRODUCTION

Cigarette smoking remains the leading cause of preventable death in the USA.^{1–3} While smoking trends have steadily decreased over the last several decades,⁴ new types of inhaled nicotine-based products – namely electronic cigarettes (‘e-cigarettes’ or electronic nicotine delivery systems) – have rapidly emerged and gained popularity among both adults and adolescents.^{5–8} E-cigarettes have faced significant scrutiny from the medical and scientific community due to the high rates at which young individuals began using these

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- It is unclear if formal tobacco treatment (pharmacotherapy and/or behavioural support) augments smoking cessation in individuals who dual use both cigarettes and e-cigarettes.

WHAT THIS STUDY ADDS

- In this cohort study including 111 823 adult outpatients who smoked, smoking cessation was more likely among e-cigarette users compared with non-users.
- Among dual users of cigarettes and e-cigarettes, individuals who received tobacco treatment had a higher likelihood of smoking cessation compared with individuals who did not receive tobacco treatment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- These data suggest that dual users of cigarettes and e-cigarettes benefit from formal tobacco treatment which should be confirmed through future trials.

products and the uncertain health effects of these products.⁹

While the potential negative consequences of e-cigarettes are well-publicised, a growing number of tobacco treatment specialists have emphasised the potential for e-cigarettes as a smoking cessation tool among current smokers.^{9–10} Indeed, an expanding body of evidence—including both randomised trials and population-based studies—suggests that e-cigarettes may be an effective smoking cessation aid.¹¹ For example, a randomised controlled trial from England found e-cigarettes to be almost twice as effective as nicotine-replacement therapy (NRT) at achieving smoking abstinence at 1 year.¹² Further, a recent Cochrane Review (based on 29 randomised trials) concluded that there is ‘moderate-certainty evidence’ that e-cigarettes increase quit rates compared with NRT.¹³ Despite this, the United States Preventative Services Taskforce (USPSTF) does not recommend e-cigarettes for smoking cessation, citing ‘insufficient’ evidence.¹⁴ A critical gap in the current literature, identified by the USPSTF and other organisations,^{14–15} is how

e-cigarettes interact with the existing standard of care, like behavioural support and pharmacotherapy, for treating tobacco dependence.¹⁶ For example, it is unclear if patients who 'dual use' cigarettes and e-cigarettes also benefit from the use of FDA-approved smoking cessation therapies.

In this longitudinal cohort study, we used prospectively maintained data from the Barnes Jewish Hospital/Washington University School of Medicine (St. Louis, Missouri, USA) electronic health record (EHR) to assess the relationship between e-cigarette use and smoking cessation. Among individuals who currently smoked, we examined the association between e-cigarette use and smoking cessation. We further examined the association between e-cigarette use with or without formal tobacco treatment methods (ie, behavioural support and/or pharmacotherapy) and smoking cessation.

METHODS

Study design

We performed a retrospective cohort study of all adults evaluated at Barnes Jewish Hospital/Washington University School of Medicine (St. Louis, Missouri, USA), one of the largest tertiary care centres in the USA. We queried all outpatient clinic encounters from 1 June 2018 until 30 June 2021 using our EHR (Epic, Verona, Wisconsin, USA). The study proposal was reviewed and approved by the Washington University in St. Louis Human Research Protection Office and Institutional Review Board.

Patient population

Our institution, in conjunction with our cancer centre (Siteman Cancer Center, St. Louis, Missouri, USA), instituted the Electronic Health Record-Enabled Evidence-based Smoking Cessation Treatment (ELEVATE) programme as part of the National Cancer Institute Cancer Moonshot Project and the Cancer Center Cessation Initiative (C3I).^{17–19} The ELEVATE programme is a hospital-wide, point-of-care, low-burden, EHR-based tool for addressing smoking cessation which has demonstrated sustained efficacy, broad reach and reduced cost compared with other traditional models of tobacco treatment (ie, specialist referral).^{18 20 21} As part of quality improvement initiatives for this programme, we collect several longitudinal data elements on patient smoking behaviours and treatment compliance in a centralised database. This resulting dataset allows us to implement a learning health system, through which we efficiently generate and translate real-world data into actionable knowledge-based practice from our EHR.²²

We queried our institutional database for all adult patients who were documented as currently smoking during outpatient clinic encounters within the prespecified study dates (June 2018–June 2020). We analysed smoking outcomes using predefined 6-month cohorts (or time blocks) which correspond to our biannual data harvests (at the end of June or December). For example, 'Cohort 1' includes all outpatients evaluated between June and December 2018 (C2=January 2019–June 2019; C3=July 2019–December 2019; C4=January 2020–June 2020). A schematic of the study design is displayed in figure 1.

Exposure and other covariates

We queried the EHR for several discrete variables related to e-cigarette use, smoking status, tobacco-related treatments and smoking cessation outcomes. Data on current e-cigarette use were obtained from the tobacco use tab within the social history section of the EHR (yes, no, blank). If e-cigarette use was undocumented,²³ patients were assumed to be non-users. From this same section, we also harvested current smoking status. Patients were excluded if a smoking assessment did not occur in the initial encounter's time block (ie, where smoking status was blank for all encounters, <5% of patients). Pack-year smoking history (a measure of the degree of nicotine dependence) was also abstracted where available.

To determine cessation treatment use, we extracted whether patients were prescribed or were documented as having a prescription for smoking cessation pharmacotherapy using medication lists at each encounter. The pharmacotherapies assessed were varenicline, bupropion (only if indicated for smoking deterrence) and NRT (gum, patch, inhaler, nasal spray or lozenge).¹⁴ We also assessed whether patients were given behavioural support by extracting this information from the social history, tobacco use section, counselling flowsheets and best practice alerts, as previously described.^{20 21} Behavioural support included receipt of brief advice or referral to counselling through Quitlines, Smokefree TXT or various phone applications (QuitGuide, QuitSTART and so on).

We also extracted several additional covariates from the EHR encounter detail tab including patient age, gender, race and comorbidities. Comorbidities were assessed using International Classification of Disease, 10th edition (ICD-10) codes from outpatient claims data to generate an Elixhauser classification score.²⁴ Additionally, clinic specialty (surgical vs medical) was defined based on whether a patient had a surgical visit within the time block.

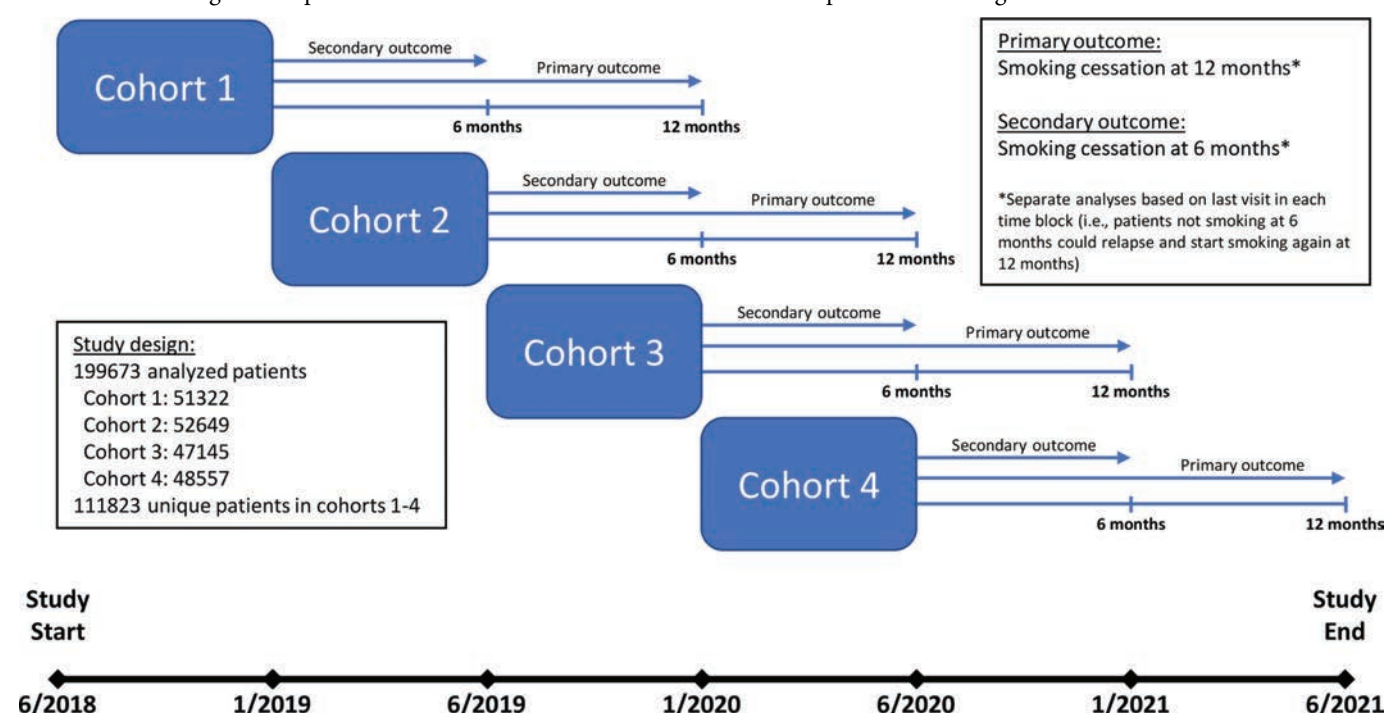


Figure 1 Study design.

Outcomes

Our outcomes were smoking cessation (point prevalence) at 6 months (secondary) and 12 months (primary). We determined smoking cessation by querying the subsequent time blocks for all adults who smoked at initial assessment. Cessation was determined based on the final assessment in each time block. For example, for Cohort 1 (6/2018–12/2018), 6-month smoking cessation was determined from the latest documented visit between 1/2019 and 6/2019; 12-month smoking cessation was determined from the latest documented visit between 7/2019 and 12/2019. If patients were not seen in the subsequent time block or if smoking status was not assessed during follow-up, these data were considered missing and assessed via penalised imputation (ie, by assuming that these patients were still smoking), as is typical of most longitudinal smoking trials.²⁵ We further verified our findings given this assumption through sensitivity analyses where 10% of patients with missing follow-up data were randomly coded to have successfully quit smoking. Of note, the 6-month and 12-month analyses were performed independently (ie, patients who stopped smoking at 6 months could have relapsed and started smoking again at 12 months).

Statistical analysis

Cohort descriptive statistics were reported based on the initial patient assessment using means (SD) for continuous variables and frequencies (proportions) for categorical variables. Cochran-Armitage tests were used to compare trends in e-cigarette use and smoking prevalence over the time blocks. Separate marginal generalised estimating equation (GEE) Poisson regression models (clustering at unique patient level) were constructed to assess factors associated with e-cigarette use (controlling for age, sex, race, comorbidities, medical service, cohort number) and factors associated with smoking cessation (controlling for same covariates and e-cigarette use). For the latter model, smoking-related comorbidities were also assessed individually. A sensitivity analysis including patients with available pack-year smoking history was used to verify that the association between e-cigarette use and smoking cessation was independent from the degree of nicotine dependence. In a separate subanalysis including only dual users of cigarettes and e-cigarettes, the association between any tobacco treatment therapy and smoking cessation was assessed using GEE Poisson regression controlling for the same covariates. P values of less than 0.05 were considered statistically significant. All analyses were performed with SAS V.9.4 (SAS Institute,

Table 1 Patient demographics

	Cohorts				Unique patients* (6/2018–6/2020) N=111 823
	Cohort 1 (6/2018–12/2018) N=51 322	Cohort 2 (1/2019–6/2019) N=52 649	Cohort 3 (7/2019–12/2019) N=47 145	Cohort 4 (1/2020–6/2020) N=48 557	
Age (n, %)					
18–40	12 822 (24.4%)	12 756 (24.2%)	11 223 (23.8%)	12 046 (24.8%)	31 481 (28.2%)
41–54	13 022 (24.7%)	13 373 (25.4%)	11 615 (24.6%)	12 108 (24.9%)	27 917 (25.0%)
55–64	14 020 (26.6%)	14 424 (27.4%)	12 891 (27.3%)	13 144 (27.1%)	28 477 (25.5%)
65+	11 458 (21.8%)	12 096 (23.0%)	11 416 (24.2%)	11 259 (23.2%)	23 948 (21.4%)
Sex (n, %)					
Male	22 751 (43.2%)	23 677 (45.0%)	21 322 (45.2%)	21 989 (45.3%)	51 104 (45.7%)
Female	28 569 (54.3%)	28 970 (55.0%)	25 820 (54.8%)	26 563 (54.7%)	60 707 (54.3%)
Race (n, %)					
White	37 667 (71.5%)	38 748 (73.6%)	35 275 (74.8%)	36 919 (76.0%)	83 415 (74.6%)
Black	11 940 (22.7%)	12 130 (23.0%)	10 680 (22.7%)	10 812 (22.3%)	24 989 (22.3%)
Other	1715 (3.3%)	1771 (3.4%)	1190 (2.5%)	826 (1.7%)	3419 (3.1%)
Total comorbidities (n, %)					
0	20 710 (40.4%)	20 938 (39.8%)	27 320 (57.9%)	39 686 (81.7%)	77 144 (69.0%)
1	15 154 (29.5%)	15 500 (29.4%)	11 032 (23.4%)	5843 (12.0%)	21 094 (18.9%)
2+	15 458 (30.1%)	16 211 (30.8%)	8793 (18.7%)	3028 (6.2%)	13 585 (12.1%)
Comorbidities (n, %)					
Hypertension	12 053 (23.5%)	12 742 (24.2%)	6892 (14.6%)	2313 (4.8%)	22 282 (19.9%)
Chronic pulmonary disease	4765 (9.3%)	5429 (10.3%)	2575 (5.5%)	717 (1.5%)	9655 (8.6%)
Diabetes	5535 (10.8%)	5913 (11.2%)	3526 (7.5%)	1044 (2.2%)	9425 (8.4%)
Peripheral vascular disease	1736 (3.4%)	1878 (3.6%)	1180 (2.5%)	545 (1.1%)	3852 (3.4%)
Congestive heart failure	1337 (2.6%)	1431 (2.7%)	805 (1.7%)	431 (0.9%)	2757 (2.5%)
Alcohol abuse	705 (1.4%)	753 (1.4%)	434 (0.9%)	162 (0.3%)	1540 (1.4%)
Pulmonary circulation disorders	155 (0.3%)	132 (0.3%)	89 (0.2%)	53 (0.1%)	353 (0.3%)
Specialty (n, %)					
Medicine	42 615 (80.9%)	44 108 (83.8%)	39 455 (83.7%)	41 787 (86.1%)	90 091 (80.6%)
Surgery	8707 (16.5%)	8541 (16.2%)	7690 (16.3%)	6770 (13.9%)	21 732 (19.4%)
E-cigarette use (n, %)					
No	50 926 (96.7%)	52 070 (98.9%)	46 306 (98.2%)	47 468 (97.8%)	109 853 (98.2%)
Yes	396 (0.8%)	579 (1.1%)	839 (1.8%)	1089 (2.2%)	1970 (1.8%)
Smoking cessation (n, %)					
6 months	6852 (13.0%)	6312 (12.0%)	5906 (12.5%)	5960 (12.3%)	16 792 (15.0%)
12 months	8841 (16.8%)	8808 (16.7%)	8009 (17.0%)	7977 (16.4%)	22 009 (19.7%)

*For unique patient counts, because one patient could appear in multiple cohorts, the information on demographics and clinical factors are displayed from the most recent cohort. 12 patients were missing a documented sex.

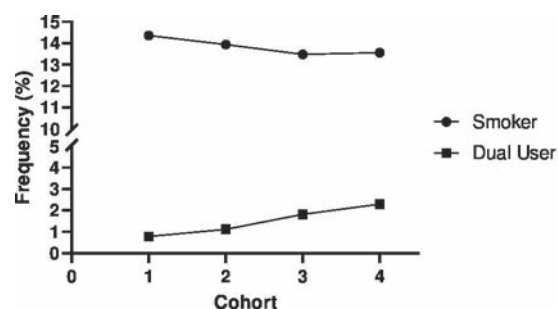


Figure 2 Trends in cigarette and e-cigarette use, 2018–2020. Smoking frequency calculated out of total number of assessed patients in each given cohort; dual user frequency calculated out of total number of smokers in each given cohort.

Cary, North Carolina, USA), Microsoft Excel (Redmond, Washington, USA) and GraphPad Prism V.9 (San Diego, California, USA).

Severe acute respiratory syndrome (SARS)

There were four articles that analysed the SARS epidemic and each showed a significant reduction in PED visits, ranging from a 36.1% to a 47% reduction. South Korea was the only country to publish articles looking at the 2015 MERS outbreak that met the inclusion criteria for this review. Summary data for SARS articles, as well as MERS articles and the four articles analysing the other epidemic diseases, can be found in online supplemental appendix 11.

Potential reasons for the reductions in PED visits during the SARS epidemic were postulated as a fear of SARS transmission,^{113 114} the influence of media coverage with phrases such as ‘killer pneumonia’¹¹⁵ or public health department advice, in this case, to stay at home when exhibiting SARS-like symptoms.¹¹⁶

RESULTS

Study population

Between June 2018 and June 2020, 111 823 unique patients who were currently smoking were included in the study. Study

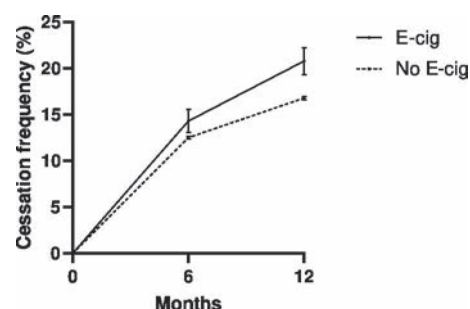


Figure 3 Smoking cessation rates at 6 and 12 months among smokers versus e-cigarette users ('dual users').

demographics are shown in table 1. The mean (SD) age was 51.2 (15.9) years old. A majority of patients were female (n=60 707, 54.3%) and of white race (n=83 415, 74.6%). In terms of documented comorbidities, 34 679 (31.0%) patients had an Elixhauser score of at least 1. The most common comorbidities were hypertension (n=22 282, 19.9%) and chronic pulmonary disease (n=9655, 8.6%). A total of 21 732 (19.4%) patients were assessed by a surgical subspecialty.

Cigarette and e-cigarette prevalence

The rate of cigarette smoking over the study period is shown in figure 2. The prevalence of cigarette smoking decreased significantly from C1 to C4 (C1 14.4%; C2 13.9%; C3 13.5%; C4 13.6%; p=0.003). Conversely, among individuals who smoked, the prevalence of dual e-cigarette use increased significantly from C1 to C4 (C1 0.8%; C2 1.1%; C3 1.8%; C4 2.3%; p<0.001). On multivariable analysis, factors associated with higher likelihood of e-cigarette use included younger age (for every 1-year increase, adjusted relative risk (aRR) 0.943, 95% CI 0.940 to 0.946, p<0.0001, online supplemental table 1), male sex (male vs female, aRR 1.117, 95% CI 1.022 to 1.222, p=0.015), white race (non-white vs white, aRR 0.374, 95% CI 0.325 to 0.431, p<0.0001), non-surgical evaluation

Table 2 Multivariable model for factors associated with smoking cessation at 6 and 12 months

	Smoking cessation at 6 months				Smoking cessation at 12 months			
	Adjusted relative risk	95% CI		P value	Adjusted relative risk	95% CI		P value
E-cigarette use								
No	(1 Reference)				(1 Reference)			
Yes	1.422	1.295	1.562	<0.0001	1.354	1.252	1.464	<0.0001
Age	1.018	1.017	1.019	<0.0001	1.014	1.014	1.015	<0.0001
Sex								
Female	(1 Reference)				(1 Reference)			
Male	0.835	0.813	0.858	<0.0001	0.843	0.823	0.863	<0.0001
Race								
White	(1 Reference)				(1 Reference)			
Non-White	1.030	0.999	1.061	0.062	0.992	0.966	1.018	0.542
Comorbidities								
0	(1 Reference)				(1 Reference)			
1	1.242	1.210	1.275	<0.0001	1.132	1.111	1.154	<0.0001
2+	1.562	1.521	1.603	<0.0001	1.314	1.289	1.340	<0.0001
Specialty								
Medicine	(1 Reference)				(1 Reference)			
Surgery	0.736	0.707	0.767	<0.0001	0.652	0.628	0.676	<0.0001
Cohort								
C1	(1 Reference)				(1 Reference)			
C2	0.938	0.916	0.959	<0.0001	1.024	1.009	1.039	0.001
C3	1.073	1.047	1.100	<0.0001	1.113	1.093	1.133	<0.0001
C4	1.211	1.178	1.244	<0.0001	1.180	1.155	1.205	<0.0001

Model controlling for age, sex, race, comorbidities, treating specialty, cohort and e-cigarette use.

Table 3 Multivariable model for factors associated with smoking cessation at 6 and 12 months among dual users of cigarettes and e-cigarettes

	Smoking cessation at 6 months			P value	Smoking cessation at 12 months			P value
	Adjusted relative risk	95% CI			Adjusted relative risk	95% CI		
Tobacco treatment								
No	(1 Reference)				(1 Reference)			
Yes	1.369	1.095	1.712	0.006	1.238	1.071	1.432	0.004
Age	1.018	1.012	1.023	<0.0001	1.015	1.010	1.019	<0.0001
Sex								
Female	(1 Reference)				(1 Reference)			
Male	0.872	0.719	1.056	0.161	0.900	0.766	1.057	0.200
Race								
White	(1 Reference)				(1 Reference)			
Non-White	0.816	0.593	1.123	0.213	0.823	0.631	1.075	0.153
Comorbidities								
0	(1 Reference)				(1 Reference)			
1	1.296	1.044	1.609	0.019	1.218	1.054	1.406	0.007
2+	1.178	0.916	1.515	0.202	1.073	0.913	1.259	0.394
Specialty								
Medicine	(1 Reference)				(1 Reference)			
Surgery	0.788	0.574	1.080	0.139	0.752	0.574	0.985	0.039
Cohort								
C1	(1 Reference)				(1 Reference)			
C2	0.793	0.604	1.040	0.094	0.975	0.828	1.149	0.765
C3	0.887	0.687	1.144	0.355	1.063	0.889	1.271	0.501
C4	0.870	0.669	1.132	0.301	1.072	0.883	1.301	0.485
Model controlling for age, sex, race, comorbidities, treating specialty, cohort and tobacco treatment								

Model controlling for age, sex, race, comorbidities, treating specialty, cohort and tobacco treatment.

(surgery vs medicine, aRR 0.689, 95% CI 0.601 to 0.790, $p<0.0001$) and more recent cohort (eg, C4 vs C1, aRR 2.385, 95% CI 2.196 to 2.591, $p<0.0001$).

E-cigarette use and smoking cessation

The overall point prevalence of tobacco cessation at 6 and 12 months after enrolment were 12.5% and 16.8%, respectively. The prevalence of smoking cessation at 12 months was higher among e-cigarette users (20.8%) compared with non- users (16.8%) (risk difference, 4.0% (95% CI, 2.5% to 5.5%); aRR 1.354, 95% CI 1.252 to 1.464, $p<0.0001$, table 2 and figure 3). The secondary outcome of smoking cessation at 6 months was also higher among e-cigarette users (14.3%) compared with non-users (12.5%) (risk difference, 1.8% (95% CI, 0.5% to 3.1%); aRR 1.422, 95% CI 1.295 to 1.562, $p<0.0001$, table 2 and figure 3).

A sensitivity analysis was performed among patients with available pack- year smoking history ($n=55\,572$, 49.7%) to verify that the association between e-cigarette use and smoking cessation was independent from the degree of nicotine dependence. In this model, e-cigarette use remained associated with higher prevalence

of smoking cessation at 12 months (aRR 1.884, 95% CI 1.602 to 2.215, $p<0.0001$, online supplemental table 2).

Combined therapy and smoking cessation

Among patients who were dual users of cigarettes and e-cigarettes, we assessed the relationship between the addition of formal tobacco treatment and smoking cessation. The point prevalence of smoking cessation at 12 months after enrolment was higher among individuals who received tobacco treatment (29.1%) compared with individuals who did not receive tobacco treatment (19.6%) (risk difference, 9.5% (95% CI, 4.6% to 14.4%); aRR 1.238, 95% CI 1.071 to 1.432, $p=0.004$, table 3 and figure 4). The secondary outcome of smoking cessation at 6 months after enrolment was also higher among individuals who received tobacco treatment (22.3%) compared with individuals who did not receive tobacco treatment (13.1%) (risk difference, 9.1% (95% CI, 4.7% to 13.6%); aRR 1.369, 95% CI 1.095 to 1.712, $p=0.006$, table 3 and figure 4).

DISCUSSION

In this study, we assessed the relationship between e-cigarette use and smoking cessation among outpatients at a large tertiary care centre in the Midwest. We found that while the prevalence of cigarette smoking decreased slightly over the study period, the prevalence of e-cigarette use among individuals who also smoked (ie, dual use) increased significantly. We further found that individuals who used e- cigarettes were more likely to stop smoking compared with individuals who did not use these products, even when controlling for the level of nicotine dependence. Finally, we identified that among patients who were dual users of both cigarettes and e-cigarettes, formal tobacco treatment with either smoking deterrent pharmacotherapy and/or behavioural support resulted in higher rates of smoking cessation. These findings suggest that individuals seen in an outpatient setting who use both cigarettes and e-cigarettes still benefit from traditional forms of tobacco treatment.

Since the recent introduction of e-cigarettes, there has been substantial debate regarding whether these products - despite

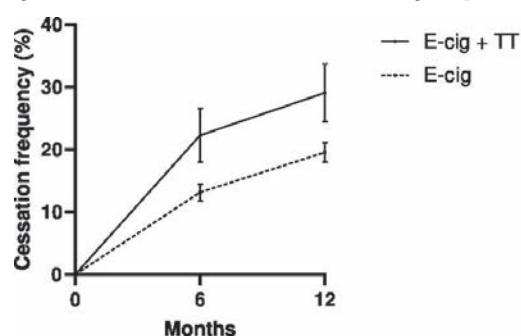


Figure 4 Smoking cessation rates at 6 and 12 months among e-cigarette users ('dual users') with versus without TT. TT, tobacco treatment.

public health concerns—help with smoking cessation.^{11–16} Most evidence examining the association between e-cigarette use and smoking cessation stems from small clinical trials (mostly outside of the USA) and population-based cohort or cross-sectional studies.^{9–10} Our study, in contrast, presents real-world data on e-cigarette use which was pragmatically harvested from our tertiary healthcare system's EHR, which also represents a geographic region with one of the highest smoking prevalences in the USA.²⁶ Through this prospectively maintained learning health system, we have been able to further validate that e-cigarette use may be beneficial to a subset of smokers who are using these products for the purposes of smoking cessation. Of course, this finding must be carefully considered in light of the unclear short-term and long-term health effects of these products.

While the prevalence of smoking has decreased over the last several decades, the proportion of U.S. adults who dual use cigarettes and e-cigarettes has increased.²⁷ Few studies have examined how traditional evidence-based forms of formal tobacco treatment (ie, behavioural support and/or pharmacotherapy) in combination with e-cigarette use affect smoking cessation outcomes in this subset of patients.¹⁶ A prior RCT examined e-cigarette use in addition to behavioural support versus behavioural support alone and found higher 7-day point prevalence abstinence at 12 weeks among e-cigarette users, although no difference was observed at 24 weeks.²⁸ Our data similarly found that dual users of cigarettes and e-cigarettes appear to benefit from formal, FDA-approved tobacco treatments to aid with smoking cessation. Future trials evaluating the efficacy of e-cigarettes for smoking cessation should assess if these products are most effective when used in combination with other FDA-approved cessation aids.¹⁶

Cigarette smoking is the leading cause of preventable death in the USA. While some studies have emphasised the harm reduction potential of e-cigarettes,²⁹ other studies have found that dual use of cigarettes and e-cigarettes is associated with worse health outcomes, including higher rates of pulmonary and cardiovascular disease.^{30–31} Therefore, in order for e-cigarettes to have any harm reducing effects, these products must be used in place of traditional cigarettes, minimising or eliminating concurrent use of both products.²⁹ Our data suggest that for patients who are dual-users of cigarettes and e-cigarettes, clinicians should routinely consider additional FDA-approved pharmacotherapy to effectively minimise this period of dual use.

This study has several strengths. Most notably, it harnesses real-world EHR data to assess e-cigarette use outside of a formal study setting. Additionally, longitudinal data on smoking status and other treatments were readily available given the data source. Conversely, this study has several limitations. First, smoking status was self-reported in this study and not biochemically confirmed. Second, we could not collect data as to whether patients continued to use e-cigarettes after smoking cessation. As discussed previously, it is important to consider the benefits of e-cigarettes for smoking cessation against the potential harms of (1) dual use and (2) long-term e-cigarette dependence. Third, given the nature of our EHR system, e-cigarette use was significantly undercaptured. For example, while we found documented e-cigarette use in 1%–2% of patients, population-based studies suggest that the prevalence of e-cigarette use in US adults is closer to 5%–8%.^{5,6,32} It may be that the assessment of dual use identified those who used e-cigarettes more frequently (ie, daily). There is evidence that more frequent users of e-cigarettes are especially likely to stop smoking.⁴ Thus, the results may be relevant to only a portion of the e-cigarette user population. Further, the increasing trend of dual use in our study may reflect better documentation as opposed to true prevalence.²³ Additional important data elements were also unavailable through the EHR, including intensity of e-cigarette use (daily vs non-daily), type of product (ie, nicotine containing) and concentration of nicotine. Fourth, we assessed comorbidities using ICD codes from outpatient claims data, which likely undercaptures comorbidities given the lack of inpatient data and limited time-frame.³³ Finally, we could not assess reasons for e-cigarette use. Others have postulated that e-cigarettes may have a benefit only in individuals who

are pursuing tobacco cessation as opposed to individuals who are using these products for pleasure.⁹ Thus, the results we obtained might reflect the effects of an intention to quit in addition to or instead of the effects of e-cigarettes per se.

In conclusion, this large cohort study demonstrated that e-cigarette use was associated with increased likelihood of smoking cessation and that formal smoking treatment methods (ie, behavioural support and/or pharmacotherapy) increased the smoking cessation rates of e-cigarette users. Our findings indicate that dual users of cigarettes and e-cigarettes may benefit from formal smoking cessation treatment as part of their healthcare.

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Contributors Study conception and design: BTH, NS, L-SC. Data acquisition and analysis: BTH, NS, GP, JC, LS-SC. **Data interpretation and manuscript writing:** BTH, NS, L-SC. Critical revision and final approval of the manuscript: all authors. L-SC is responsible for the overall content as the guarantor.

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Patient consent for publication Not applicable.

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**PROTEJA
O SEU DOENTE
EM TODAS AS FASES
DA DPOC^{1,2}**

**TRAVA
antes que
seja tarde**

**1 em cada 5 doentes
morre no período de 1 ano*
após a primeira exacerbação com
necessidade de hospitalização.³
Não perca mais tempo.**

*após alta hospitalar



**BEVESPI
AEROSPHERE®**

(glicopirrônio/fumarato de formoterol)
Suspensão Pressurizada para Inalação

DPOC, doença pulmonar obstrutiva crônica

Referências: 1. Riltrava Aerosphere 5 microgramas/7,2 microgramas/160 microgramas, suspensão pressurizada para inalação [Resumo das Características do Medicamento]. AstraZeneca AB, SE-151 85 Södertälje Suécia; abril 2022. Acedido em www.infarmed.pt em outubro 2022. 2. Bevespi Aerosphere 5 microgramas/7,2 microgramas, suspensão pressurizada para inalação [Resumo das Características do Medicamento]. AstraZeneca AB, SE-151 85 Södertälje Suécia; agosto 2022. Acedido em www.infarmed.pt em outubro 2022. 3. Ho T-W, Tsai Y-J, Ruan S-Y, et al. In-Hospital and One-Year Mortality and Their Predictors in Patients Hospitalized for First-Ever Chronic Obstructive Pulmonary Disease Exacerbations: A Nationwide Population-Based Study. *Bai C, editor. PLoS ONE*. 2014 Dec;9(12):e114866.

Informações essenciais compatíveis com o Resumo das Características do Medicamento

Bevespi Aerosphere 7,2 microgramas/5 microgramas, suspensão pressurizada para inalação. Cada dose única (dose libertada que sai do aplicador bucal) contém 9 microgramas de brometo de glicopirrônio, equivalente a 7,2 microgramas de glicopirrônio, e 5 microgramas de fumarato de formoterol di-hidratado. Isto corresponde a uma dose calibrada de 10,4 microgramas de brometo de glicopirrônio, equivalente a 8,3 microgramas de glicopirrônio, e 5,8 microgramas de fumarato de formoterol di-hidratado. **Indicações terapêuticas:** Bevespi Aerosphere é indicado como tratamento broncodilatador de manutenção para o alívio de sintomas em doentes adultos com doença pulmonar obstrutiva crônica (DPOC). **Posologia e modo de administração:** **Posologia:** A dose recomendada é duas inalações duas vezes por dia (duas inalações de manhã e duas inalações à noite). Os doentes devem ser aconselhados a não fazer mais de 2 inalações duas vezes por dia. Se for omitida uma dose, esta deve ser tomada assim que for possível e a dose seguinte deve ser tomada no horário habitual. Não deve tomar-se uma dose a dobrar para compensar uma dose esquecida. **Populações especiais:** **Idosos:** Não é necessário qualquer ajuste de dose em doentes idosos. **Compromisso renal:** Bevespi Aerosphere pode ser utilizado na dose recomendada em doentes com compromisso renal ligeiro a moderado. Em doentes com compromisso renal grave ou com doença renal em fase terminal com necessidade de diálise, só deve ser utilizado se o benefício esperado for superior ao risco potencial. **Compromisso hepático:** Bevespi Aerosphere pode ser utilizado na dose recomendada em doentes com compromisso hepático ligeiro a moderado. Não existem dados relevantes sobre a utilização de Bevespi Aerosphere em doentes com compromisso hepático grave e o medicamento deve ser utilizado com precaução nestes doentes. **População pediátrica:** Não existe utilização relevante de Bevespi Aerosphere em crianças e adolescentes (com idade inferior a 18 anos) para a indicação de DPOC. **Modo de administração:** Utilização por via inalatória. **Instruções de utilização:** Ao acionar Bevespi Aerosphere, um volume de suspensão é expelido do recipiente pressurizado a alta velocidade. Quando o doente inala através do aplicador bucal ao mesmo tempo que aciona o inalador, a substância segue o ar inspirado para as vias respiratórias. Os doentes devem ser instruídos sobre a técnica de inalação correta. É importante instruir o doente para: Ler com atenção as instruções de utilização no folheto informativo, que se encontra dentro da embalagem de cada inalador. Não utilizar o inalador se o agente excicante, contido na bolsa de alumínio, tiver vazado da sua embalagem. Preparar o inalador agitando-o e acionando-o quatro vezes para o ar antes da primeira utilização ou duas vezes quando o inalador não tenha sido utilizado há mais de sete dias, tenha sido exposto a temperaturas baixas ou tenha caído. Para obter uma deposição pulmonar adequada das substâncias ativas, o carregamento da dose tem de ser coordenado com a inalação. Doentes com dificuldade em coordenar o carregamento da dose com a inspiração podem utilizar Bevespi Aerosphere com uma câmara expansora para garantir a administração adequada do produto. Foi demonstrada compatibilidade com a câmara expansora Aerochamber Plus Flow-Vu. **Contra-indicações:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **Advertências e precauções especiais de utilização:** **Asma:** Bevespi Aerosphere não deve ser utilizado no tratamento da asma. **Broncospasmo paradoxal:** Se ocorrer broncospasmo paradoxal, o tratamento com o medicamento deve ser interrompido e devem ser considerados outros tratamentos. **Não indicado para utilização em situações agudas:** Bevespi Aerosphere não é indicado para o tratamento de episódios agudos de broncospasmo, isto é, como terapêutica de alívio. **Efeitos cardiovasculares:** Podem ser observados efeitos cardiovasculares, após a administração de antagonistas dos receptores muscarínicos e simpaticomiméticos, incluindo glicopirrônio ou formoterol. Bevespi Aerosphere deve ser utilizado com precaução em doentes com doenças cardiovasculares graves, tais como cardiopatia isquémica, taquiarritmias ou insuficiência cardíaca grave. Recomenda-se também precaução em doentes com tireotoxicose ou com prolongamento do intervalo QTc conhecido ou suspeito. **Hipocalcemia:** Os agonistas β_2 -adrenérgicos podem causar hipocalcemia significativa, o que pode aumentar a suscetibilidade para arritmias cardíacas. A diminuição do potássio sérico é normalmente transitória, não necessitando de suplementação. Em doentes com DPOC grave, a hipocalcemia pode ser potenciada por hipoxia e tratamento concomitante. **Hiperglicemia:** A inalação de doses elevadas de agonistas β_2 -adrenérgicos pode provocar o aumento da glicose plasmática. **Atividade anticolinérgica:** Devido à sua atividade anticolinérgica, Bevespi Aerosphere deve ser utilizado com precaução em doentes com hiperplasia da próstata sintomática, retenção urinária ou glaucoma de ângulo fechado. **Compromisso renal:** Como o glicopirrônio é excretado predominantemente por via renal, os doentes com compromisso renal grave (depuração de creatinina <30 ml/min), incluindo aqueles com doença renal em fase terminal com necessidade de diálise, apenas devem ser tratados com Bevespi Aerosphere se o benefício esperado superar o risco potencial. **Compromisso hepático:** Em doentes com compromisso hepático grave, Bevespi Aerosphere só deve ser utilizado se o benefício esperado superar o risco potencial. Estes doentes devem ser monitorizados para potenciais reações adversas. **Interações medicamentosas e outras formas de interação:** **Interações farmacocinéticas:** O potencial para interações metabólicas é considerado baixo. Como o glicopirrônio é eliminado principalmente por via renal, podem ocorrer potencialmente interações medicamentosas com medicamentos que afetam os mecanismos de excreção renal. **Interações farmacodinâmicas:** Outros antimuscarínicos e simpaticomiméticos: A coadministração de Bevespi Aerosphere com outros medicamentos contendo anticolinérgicos e/ou agonistas β_2 -adrenérgicos de longa duração de ação não foi estudada e não é recomendada uma vez que poderá potenciar as reações adversas conhecidas dos antagonistas muscarínicos ou dos agonistas β_2 -adrenérgicos inalados. Não existe evidência clínica de interações quando utilizado concomitantemente com outros medicamentos para a DPOC, incluindo broncodilatadores β_2 -adrenérgicos de curta duração de ação, metilxantinas e esteróides orais e inalados. **Hipocalcemia induzida por fármacos:** O tratamento concomitante com derivados da metilxantina, esteróides ou diuréticos não poupadores de potássio pode potenciar o possível efeito hipocalcémico inicial dos agonistas β_2 -adrenérgicos, pelo que se recomenda precaução na sua utilização concomitante. **Bloqueadores β_2 -adrenérgicos:** Os bloqueadores β_2 -adrenérgicos (incluindo colírios) podem atenuar ou inibir o efeito dos agonistas β_2 -adrenérgicos, tal como o formoterol. O uso simultâneo de bloqueadores β_2 -adrenérgicos não seletivos ou seletivos deve ser evitado, a não ser que existam razões determinantes para a sua utilização. Se forem necessários bloqueadores β_2 -adrenérgicos (incluindo colírios), dê-se preferência a bloqueadores β_2 -adrenérgicos cardiosseletivos, embora também estes devam ser administrados com precaução. **Outras interações farmacodinâmicas:** Bevespi Aerosphere deve ser administrado com precaução em doentes que estejam a ser tratados com medicamentos conhecidos por prolongar o intervalo QTc. **Fertilidade, gravidez e aleitamento:** **Gravidez:** Não existem dados sobre a utilização de Bevespi Aerosphere em mulheres grávidas. Bevespi Aerosphere só deve ser utilizado durante a gravidez se os benefícios esperados superarem os potenciais riscos. **Amamentação:** Não é conhecido se o glicopirrônio ou o formoterol são excretados no leite humano. A administração de Bevespi Aerosphere a mulheres que estão a amamentar só deve ser considerada se o benefício esperado para a mãe for superior a qualquer possível risco para o bebé. **Fertilidade:** Considera-se pouco provável que Bevespi Aerosphere, administrado na dose recomendada, afete a fertilidade no ser humano. **Efeitos indesejáveis:** **Frequentes:** Ansiedade, Cefaleia, Tonturas, Boca seca, Náuseas, Espasmos musculares, Infecção do trato urinário, Dor torácica. **Pouco frequentes:** Reações de hipersensibilidade, incluindo erupção cutânea e prurido, Hiperglicemia, Agitação, Irrequietude, Insónia, Tremor, Taquicardia, Palpitações, Arritmias cardíacas (fibrilhação

auricular, taquicardia supraventricular e extra-sístoles), Retenção urinária. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas através do Sítio da internet: <http://www.infarmed.pt/web/infarmed/submissaoar> (preferencialmente) ou através dos seguintes contactos: Direção de Gestão do Risco de Medicamentos: (Tel.: +351217987373; Linha do Medicamento: 800222444 (gratuita); E-mail: farmacovigilancia@infarmed.pt). **Titular da Autorização de Introdução no Mercado:** AstraZeneca AB, SE-151 85 Södertälje, Suécia. **Representante local do Titular da Autorização de Introdução no Mercado:** Tecnimed - Sociedade Técnico-Medicinal, S.A., Rua da Tapada Grande, n.º 2, Abrunheira, 2710-089 Sintra. Informações revistas em agosto 2022. **Para mais informações deverá contactar o representante local do Titular da Autorização de Introdução no Mercado. Medicamento sujeito a receita médica. Medicamento compartilhado pelo Escalão B (69% de comparticipação no regime geral e 84% de comparticipação no regime especial). Versão 1.0 (agosto 2022).**

Informações essenciais compatíveis com o Resumo das Características do Medicamento

Riltrava Aerosphere 5 microgramas/7,2 microgramas/160 microgramas, suspensão pressurizada para inalação. Cada dose única (dose libertada que sai do aplicador bucal) contém 5 µg de fumarato de formoterol di-hidratado, 9 µg de brometo de glicopirrónio, equivalente a 7,2 µg de glicopirrónio e 160 µg de budesonida. Isto corresponde a uma dose calibrada de 5,3 µg de fumarato de formoterol di-hidratado, 9,6 µg de brometo de glicopirrónio, equivalente a 7,7 µg de glicopirrónio e 170 µg de budesonida. **Indicações terapêuticas:** Riltrava Aerosphere é indicado como tratamento de manutenção em doentes adultos com DPOC moderada a grave, que não estão adequadamente tratados com uma associação de um corticosteroide inalado e um agonista beta2 de longa duração de ação ou uma associação de um agonista beta2 de longa duração de ação e um antagonista muscarínico de longa duração de ação. **Posologia e modo de administração:** **Posologia:** A dose recomendada e máxima é de 2 inalações 2x/dia (2 inalações de manhã e 2 inalações à noite). Se for omitida uma dose, esta deve ser tomada assim que for possível e a dose seguinte deve ser tomada no horário habitual. Não se deve tomar uma dose a dobrar para compensar uma dose esquecida. **Populações especiais:** **Idosos:** Não é necessário qualquer ajuste de dose em doentes idosos. **Compromisso renal:** Este medicamento pode ser utilizado na dose recomendada em doentes com compromisso renal ligeiro a moderado. Pode também ser utilizado na dose recomendada em doentes com compromisso renal grave ou com doença renal em fase terminal com necessidade de diálise, apenas se o benefício esperado for superior ao risco potencial. **Compromisso hepático:** Este medicamento pode ser utilizado na dose recomendada em doentes com compromisso hepático ligeiro a moderado. Pode também ser utilizado na dose recomendada em doentes com compromisso hepático grave, o medicamento deve ser utilizado apenas se o benefício esperado for superior ao risco potencial. **População pediátrica:** Não existe utilização relevante deste medicamento em crianças e adolescentes (com idade inferior a 18 anos) para a indicação da DPOC. **Modo de administração:** Para utilização por via inalatória. **Instruções de utilização:** De forma a assegurar uma administração correta do medicamento, o médico ou outro profissional de saúde deve demonstrar ao doente como utilizar corretamente o inalador, e deve monitorizar regularmente a técnica de inalação do doente. O doente deve ser aconselhado a ler com atenção o Folheto Informativo e seguir as instruções de utilização conforme indicado no mesmo. Ao acionar Riltrava Aerosphere, um volume de suspensão é expelido do recipiente pressurizado. Quando o doente inala através do aplicador bucal ao mesmo tempo que aciona o inalador, a substância segue o ar inspirado para as vias respiratórias. Os doentes que têm dificuldade em coordenar o acionamento com a inalação podem utilizar Riltrava Aerosphere com uma câmara expansora para garantir a administração adequada do medicamento. Pode ser utilizado com câmaras expansoras incluindo o Aerochamber Plus FlowVu. **Contraindicações:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **Advertências e precauções especiais de utilização:** **Não indicado para utilização em situações agudas.** Este medicamento não é indicado para o tratamento de episódios agudos de broncospasma, isto é, como terapêutica de alívio. **Broncospasma paradoxal:** A administração de formoterol/glicopirrónio/budesonida pode produzir broncospasma paradoxal com sibilos e dispnéia imediatamente após a administração e pode ser potencialmente fatal. O tratamento com este medicamento deve ser imediatamente interrompido se ocorrer broncospasma paradoxal. O doente deve ser avaliado e instituído tratamento alternativo, se necessário. **Deterioração da doença:** Recomenda-se que o tratamento com este medicamento não seja interrompido abruptamente. Se os doentes não considerarem o tratamento eficaz, devem manter o tratamento, mas tem de se procurar aconselhamento médico. O aumento da utilização de broncodilatadores de alívio indica um agravamento do quadro clínico subjacente e justifica uma reavaliação da terapêutica. A deterioração rápida e progressiva nos sintomas da DPOC é potencialmente fatal e o doente deve ser submetido a avaliação médica urgente. **Efeitos cardiovasculares:** Podem ser observados efeitos cardiovasculares, tais como arritmias cardíacas, p.ex. fibrilação auricular e taquicardia, após a administração de antagonistas dos receptores muscarínicos e simpaticomiméticos, incluindo glicopirrónio e formoterol. Este medicamento deve ser utilizado com precaução em doentes com doença cardiovascular grave não controlada e clinicamente significativa, tal como cardiopatia isquémica instável, enfarte agudo do miocárdio, cardiomiopatia, arritmias cardíacas, e insuficiência cardíaca grave. Recomenda-se também precaução ao tratar doentes com prolongamento do intervalo QTc (QTc > 450 milissegundos para homens ou > 470 milissegundos para mulheres), conhecido ou suspeito, quer seja congénito ou induzido por medicamentos. **Efeitos sistémicos com corticosteroides:** Podem ocorrer efeitos sistémicos com qualquer corticosteroide inalado, particularmente em doses elevadas prescritas por longos períodos de tempo. Estes efeitos são muito menos prováveis de ocorrer com o tratamento por inalação do que com corticosteroides orais. Os efeitos sistémicos possíveis incluem síndrome de Cushing, manifestações Cushingoides, supressão suprarrenal, diminuição da densidade mineral óssea, cataratas e glaucoma. Devem ser considerados efeitos potenciais na densidade óssea especialmente com a administração de doses elevadas durante longo período de tempo em doentes com fatores de risco coexistentes para osteoporose. **Perturbações visuais:** Podem ser notificadas perturbações visuais com a utilização sistémica e tóxica de corticosteroides. Se um doente apresentar sintomas tais como visão turva ou outras perturbações visuais, o doente deve ser encaminhado para um oftalmologista para avaliação de possíveis causas que podem incluir cataratas, glaucoma ou doenças raras, tais como CRSC, que foram notificadas após a utilização de corticosteroides sistémicos e tópicos. **Transfusão de terapêutica oral:** Recomenda-se atenção especial nos doentes que fazem a transição de esteróides orais, uma vez que podem continuar em risco de compromisso da função suprarrenal durante um período de tempo considerável. Os doentes que necessitam de terapêutica com doses elevadas de corticosteroides ou tratamento prolongado com a dose mais elevada recomendada de corticosteroides inalados, podem estar igualmente em risco. Estes doentes podem apresentar sinais e sintomas de insuficiência suprarrenal quando expostos a stress grave. Deve ser considerada cobertura adicional com corticosteroides sistémicos durante períodos de stress ou cirurgia eletiva. **Pneumonia em doentes com DPOC:** Tem sido observado um aumento na incidência de pneumonia, incluindo pneumonia que requer hospitalização, nos doentes com DPOC a receberem corticosteroides inalados. Existe alguma evidência de risco aumentado de pneumonia com o aumento da dose de esteroide, não tendo sido demonstrado de forma conclusiva nos diversos estudos. Não existe evidência clínica conclusiva para diferenças dentro da mesma classe na magnitude do risco de pneumonia entre os medicamentos contendo corticosteroides inalados. Os médicos devem continuar alerta para o possível desenvolvimento de pneumonia em doentes com DPOC pois as características clínicas de tais infeções sobrepõem-se aos sintomas das exacerbações da DPOC. Os fatores de risco para pneumonia em doentes com DPOC incluem tabagismo atual, idade avançada, IMC baixo e DPOC grave. **Hipocalcemia:** A hipocalcemia potencialmente grave pode resultar da terapêutica com agonistas-β. Estes têm o potencial de produzir acontecimentos cardiovasculares adversos. Recomenda-se precaução especial na DPOC grave, pois esse efeito pode ser potencializado pela hipoxia. A hipocalcemia também pode ser potencializada pelo tratamento concomitante com outros medicamentos que podem induzir hipocalcemia, tais como derivados de xantinas, esteróides e diuréticos. **Hiperglicemia:** A inalação de doses elevadas de agonistas β₂-adrenérgicos pode provocar o aumento da glucose plasmática. A glicemia deve ser monitorizada durante o tratamento de acordo com as orientações estabelecidas para doentes com diabetes. **Condições coexistentes:** Este medicamento deve ser utilizado com precaução em doentes com tireotoxicose. **Atividade anticolinérgica:** Devido à sua atividade anticolinérgica, este medicamento deve ser utilizado com precaução em doentes com hiperplasia da próstata sintomática, retenção urinária ou glaucoma de ângulo fechado. Os doentes devem ser informados sobre os sinais e sintomas do glaucoma de ângulo fechado e devem ser informados para interromper a utilização deste medicamento e contactar o seu médico imediatamente, caso algum destes sinais ou sintomas se desenvolvam. Não é recomendada a administração concomitante deste medicamento com outros medicamentos contendo anticolinérgicos. **Compromisso renal:** Como o glicopirrónio é excretado predominantemente por via renal, os doentes com compromisso renal grave (depuração de creatinina <30 ml/min), incluindo aqueles com doença renal em fase terminal com necessidade de diálise, apenas devem ser tratados com este medicamento se o benefício esperado superar o risco potencial. **Compromisso hepático:** Em doentes com compromisso hepático grave, este medicamento só deve ser utilizado se o benefício esperado superar o risco potencial. Estes doentes devem ser monitorizados para potenciais reações adversas. **Interações medicamentosas e outras formas de interação:** **Interações farmacodinâmicas:** Prevê-se que o tratamento em associação com inibidores potentes do CYP3A, por exemplo itraconazol, cetoconazol, inibidores de protease do VIH e medicamentos que contêm cobicistate, aumente o risco de efeitos indesejáveis sistémicos, e deve ser evitado, a não ser que o benefício seja superior ao risco aumentado de reações adversas aos corticosteroides sistémicos, nesse caso os doentes devem ser monitorizados para reações adversas aos corticosteroides sistémicos. Este facto é de relevância clínica limitada em tratamentos de curta duração (1-2 semanas). Como o glicopirrónio é eliminado principalmente por via renal, podem ocorrer potencialmente interações medicamentosas com medicamentos que afetam os mecanismos de excreção renal. **Interações farmacodinâmicas:** **Outros antimuscarínicos e simpaticomiméticos:** A administração concomitante deste medicamento com outros medicamentos contendo anticolinérgicos e/ou agonistas β₂-adrenérgicos de longa duração de ação não foi estudada e não é recomendada uma vez que poderá potenciar as reações adversas conhecidas dos antagonistas muscarínicos ou dos agonistas β₂-adrenérgicos inalados. A utilização concomitante de outros medicamentos beta-adrenérgicos pode ter efeitos potencialmente aditivos; portanto é necessário precaução quando outros medicamentos beta-adrenérgicos são prescritos concomitantemente com formoterol. **Hipocalcemia induzida por medicamentos:** A hipocalcemia pode aumentar a disposição para arritmias em doentes que são tratados com glicosídeos digitálicos. **Bloqueadores β-adrenérgicos:** Os bloqueadores β-adrenérgicos (incluindo colírios) podem atenuar ou inibir o efeito do formoterol. O uso simultâneo de bloqueadores β-adrenérgicos deve ser evitado, a não ser que o benefício esperado ultrapasse o risco potencial. Se forem necessários bloqueadores β-adrenérgicos, dá-se preferência a bloqueadores β-adrenérgicos cardiosseletivos. **Outras interações farmacodinâmicas:** O tratamento concomitante com quinidina, disopiramide, procainamida, anti-histamínicos, inibidores da monoamina oxidase, antidepressivos tricíclicos e fenotiazinas pode prolongar o intervalo QT e aumentar o risco de arritmias ventriculares. Além disso, L-dopa, L-tirosina, oxitocina e álcool podem prejudicar a tolerância cardíaca aos beta2-simpaticomiméticos. O tratamento concomitante com inibidores da monoamina oxidase, incluindo medicamentos com propriedades semelhantes como furazolidona e procabazina, pode dar origem a reações hipertensivas. Existe um risco elevado de arritmias em doentes a receberem anestesia concomitante com hidrocarbonetos halogenados. **Fertilidade, gravidez e aleitamento:** A administração deste medicamento a mulheres grávidas só deve ser considerada se o benefício esperado para a mãe justificar o potencial risco para o feto. A administração deste medicamento a mulheres que estão a amamentar só deve ser considerada se o benefício esperado para a mãe for superior a qualquer possível risco para a criança. Considera-se pouco provável que este medicamento administrado na dose recomendada, afete a fertilidade no ser humano. **Efeitos indesejáveis:** **Frequentes:** Candidíase oral; Pneumonia; Hiperglicemia; Ansiedade; Insónia; Cefaleia; Palpitações; Disfonia; Tosse; Náuseas; Espasmos musculares; Infecção do trato urinário. **Pouco frequentes:** Hipersensibilidade; Depressão; Agitação; Irrequietude; Nervosismo; Tonturas; Tremor; Angina de peito; Taquicardia; Arritmias cardíacas (fibrilação auricular, taquicardia supraventricular e extrasístoles); Irritação da garganta; Broncospasma; Boca seca; Equimose; Retenção urinária; Dor torácica. **Muito raros:** Sinais ou sintomas de efeitos sistémicos de glucocorticóides, por exemplo supressão suprarrenal; Comportamento anormal. **Desconhecido:** Angioedema; Visão turva; Cataratas; Glaucoma. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas através do Sítio da internet: <http://www.infarmed.pt/web/infarmed/submissaoar> (preferencialmente) ou através dos seguintes contactos: Direção de Gestão do Risco de Medicamentos: (Tel.: +351 21 798 73 73; Linha do medicamento: 800 222 444 (gratuita); E-mail: farmacovigilancia@infarmed.pt). **Titular da Autorização de Introdução no Mercado:** AstraZeneca AB, SE-151 85 Södertälje, Suécia. **Representante local do Titular da Autorização de Introdução no Mercado:** Tecnimed - Sociedade Técnico-Medicinal, S.A., Rua da Tapada Grande, n.º 2, Abrunheira, 2710-089 Sintra. Informações revistas em abril 2022. **Para mais informações deverá contactar o representante local do Titular da Autorização de Introdução no Mercado. Medicamento sujeito a receita médica. Medicamento compartilhado pelo Escalão B (69% de comparticipação no regime geral e 84% de comparticipação no regime especial). 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ARTIGO ORIGINAL

Utilizar uma aplicação para smartphone mantém a atividade física na sequência da reabilitação pulmonar em pacientes com DPOC: um ensaio aleatorizado com controlo

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RESUMO

Contexto As evidências sugerem que os pacientes com DPOC sentem dificuldade em manter uma atividade física (AF) melhorada depois de terminar a reabilitação pulmonar (RP). As aplicações para smartphone (apps) que oferecem um programa de treino abrangente conferiram benefícios à saúde. Este estudo foi realizado para determinar se a utilização regular de uma app mantém a AF após a RP.

Métodos Foram inscritos pacientes com DPOC de estágio II-IV num ensaio de 6 meses após RP. Após o período de rastreio, os participantes foram aleatoriamente divididos pelo grupo da app DPOC Kaia (grupo de intervenção (GI)) ou pelo grupo de controlo (GC). O resultado primário foi AF (passos diários) medida com recurso a um monitor de atividade. Os resultados secundários incluíram Teste de Avaliação de DPOC (CAT), Questionário de Doença Respiratória Crónica (CRQ) e Teste Sit-to-Stand de 1 min (STST).

Resultados Sessenta participantes concluíram o estudo. Os passos médios do cenário de base aos 6 meses foram significativamente diferentes entre os grupos, a favor do GI (−105,3, IQR −197,0, 1 a 2105,8, vs. GC −1173,0, IQR −3813,1 a −93,8; $p=0,007$). O CAT foi significativamente reduzido no GI (15,1 ± 8,6 vs. 19,7 ± 6,4, $p=0,02$), ao passo que os subdomínios CRQ de dispneia (4,5 ± 1,7 vs. 3,7 ± 1,3, $p=0,033$) e de cansaço (4,5 ± 1,4 vs. 3,5 ± 1,3, $p=0,028$) melhoraram significativamente no GI. O STST aos 6 meses não foi significativo. A duração do sono e a duração da eficácia não apresentaram diferenças significativas entre os dois grupos em qualquer altura.

Conclusões Um programa abrangente de utilização da app Kaia após RP manteve a AF e melhorou os sintomas de pacientes com DPOC aos 6 meses. A app poderá ser uma ferramenta acessória importante para o cuidado melhorado da DPOC.

Número de registo do ensaio DRKS00017275.

INTRODUCTION

Pulmonary rehabilitation (PR) is defined as a multidisciplinary and comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education and behavioural changes designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote long-term adherence to health-enhancing behaviours.¹ PR is considered an important modality for non-pharmacological management of COPD. Numerous trials have shown that participation in a PR programme improves health-related quality of life (HRQoL) and exercise capacity in patients

Key messages

What is the key question?

► To date, no study has been able to demonstrate the benefits of eHealth in the postrehabilitation phase, especially in terms of maintaining physical activity (PA) in patients with COPD.

What is the bottom line?

► Regular use of the contents of the smartphone application (app) Kaia COPD app not only maintained PA in patients with COPD after rehabilitation but also improved symptoms.

Why read on?

► Widespread use of eHealth has the potential to close the long-known gap in postrehabilitation.

with COPD.² However, it is often challenging for patients with COPD who have completed a PR programme to maintain physical activity (PA) and to integrate regular exercise training into their daily lives. Consequently, many patients with COPD fail to adhere to exercise training after completing PR and receive insufficient instructions to continue their exercise training at home.³

A systematic review and meta-analysis of single-group and randomised trials evaluating the effect of exercise training (not necessarily PR) on PA concluded that this intervention conferred a small but significant increase in this outcome.⁴ Studies have highlighted the crucial importance of maintaining PA in COPD showing significantly higher survival rates correlated with increased PA.^{5,6} Several studies confirmed that a sustainable increase in PA following PR in patients with COPD with declining levels of PA is inconsistent following structured PR programmes.^{7,8}

Digital therapeutics to promote behavioural change in chronic conditions have recently emerged with a growing body of evidence supporting their use across many indications.⁹ Of note, digital rehabilitation tools have been suggested as a means of increasing access to rehabilitation and structured exercise in different indications.^{10,11} Recent studies have investigated the effect of short-course digital interventions for PR in COPD, comparing them



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against face-to-face outpatient PR, which demonstrated comparable results in terms of HRQoL and exercise capacity as measured by the 6 min walk test.¹² Further pilot studies have suggested the potential of digital applications (app) to also improve HRQoL and to reduce hospital readmissions in patients with severe symptoms when compared with standard care.¹³ Another pilot study suggested a moderate improvement in HRQoL in newly diagnosed COPD, regardless of disease severity.¹⁴ The effect of mobile health (mHealth) app use on PA was also investigated in an early feasibility mixed-methods study, but the effect of app usage on PA was not detected.¹⁵

The Kaia COPD app is available as a digital solution for PR and consists of an exercise training programme, breathing exercises and an educational programme.¹⁶ To the best of the authors' knowledge, no current evidence supports the use of digital health interventions following structured PR programme PA. We hypothesised that the use of this smartphone app would maintain PA in patients with COPD following PR.

METHODS

Participants and study centres

This trial was conducted as an international, bicentre, parallel-group randomised controlled trial (RCT). Study participants were in COPD Global Initiative for Obstructive Lung Disease (GOLD) stages II–IV who were randomised in a 1:1 ratio in parallel assignment to either the intervention group (IG), which was provided with the Kaia COPD app, or the control group (CG), which received standard care (accomplished by using a software randomiser, <https://www.randomizer.org>). Two centres specialised in inpatient PR for COPD (Schoen Klinik Berchtesgaden Land, Germany, and Zurich RehaCenter Clinic Wald, Switzerland) recruited participants. The trial was reported in line with the Consolidated Standards of Reporting Trials recommendations for the reporting of RCTs.¹⁷

The study was registered with the German Clinical Trials Register. A summary of the study protocol has been published.¹⁸

Objectives and outcomes

The primary objective was to assess the effectiveness of the newly developed COPD app as a maintenance programme after PR. The primary outcome was defined as a change in PA, measured in steps per day after 6 months. A commonly used activity tracker (POLAR A370 watch; Polar Electro Europe AG, Steinhausen, Switzerland) was used to measure the results of the primary endpoint. In a previous study, this activity tracker was also shown to be valid for daily life assessment of PA in patients with COPD.¹⁹

The secondary objectives were to evaluate the effects of the COPD app programme on functional exercise capacity (1 min Sit-to-Stand Test (STST)²⁰), HRQoL and patient-reported health status (Chronic Respiratory Disease Questionnaire (CRQ)²¹ and COPD Assessment Test (CAT)²²), number of exacerbations (defined as an increase in symptoms and an increase in dosage of or a new prescription of systemic corticosteroids and/or antibiotics), and depression and anxiety symptoms (Hospital Anxiety and Depression Scale²³). Furthermore, we aimed to investigate patients' compliance, adherence and safety; to identify factors that facilitate the implementation of the programme in the patient's home setting; and to evaluate factors of the programme that are especially supportive of patient care. For additional information regarding materials and methods, see online supplemental material.

Intervention

The study intervention consisted of physical exercise training sessions conducted daily by the patient via the Kaia COPD app. The app is available as a digital solution for PR in German-speaking countries. This COPD app consisted of an exercise training programme, breathing exercises and an educational programme, and was developed by healthcare professionals and PR experts. In a feasibility study for the Kaia app, promising results were obtained from a 20-day intervention on the CAT and HRQoL in patients with severely symptomatic COPD.¹⁶

Regular contacts via telephone calls were made by a trained healthcare professional to assess and discuss compliance with the study intervention. Additionally, patients were contacted by phone if they did not meet the predefined minimal adherence criteria (exercising with the app at least 4 out of 7 days a week).

Individualised strength training programme

The exercise training programme provided by the COPD app consisted of various daily whole-body exercises of 15–20 min. Most exercises included compound movements to train large muscle groups and improve upper and lower body strength and mobility. Each exercise day began with a whole-body warm-up and finished with two to three stretching exercises. During the programme, the intensity of the exercises was progressively increased dynamically based on patient feedback recorded through the application at the end of each exercise session. All exercises were explained in exercise videos, which included detailed instructions to ensure proper performance, training amount and intensity. Completed training sessions were recorded by the application, and aggregated data about training intensity and frequency were provided to the site staff to assess compliance with the study intervention. Within the exercise training programme, frequency of workouts, as well as exercise duration and intensity, were initially determined using a self-test assessing baseline exercise capacity. All exercises were performed without the need for specialised exercise equipment. Furthermore, the app promoted overall PA (eg, walking). The number of steps per day was collected by the activity tracker and reported to the app, and goals for activity were set weekly, depending on the updated individual fitness level. Users were reminded of their activity goals via push notifications provided by the app. The CG also wore the activity tracker every day and used a smartphone for the assessments but had no access to the COPD app. The IG and CG received a leaflet to encourage an active lifestyle (German version of 'living well with COPD') as well as individual exercise recommendations, as part of their discharge instructions to reflect the established standard of care. At the 6-month assessment, participants who were allocated to the CG were offered to use the Kaia COPD app free of charge.

Sample size calculation and statistics

Sample size calculation was based on expected changes in the primary endpoint and the average step difference between the groups from week 1 to the 6-month follow-up. The minimal clinically important difference in steps per day after PR is estimated between 350 and 1100 steps as measured with an activity tracker during an intervention.²⁴ Assuming an SD of the outcome variable of 2500 steps/day, an expected effect size of 2000 steps/day could be assumed for programmes combining PA counselling with PR to increase activity. According to a current meta-analysis,²⁵ to achieve 80% power and a significance level of 5% (one-sided), a sample size of 52 participants (26 participants in each group) was required. Assuming a drop-out rate of 50%, enrolment of up to 104 participants was expected. From our study group, two RCTs on outpatient training interventions were published in advance, each demonstrating high drop-out rates of 45% and 57%.^{26,27} The sample calculation and the primary outcome analysis were based on a two-tailed unpaired t-test comparing changes from baseline between the two groups at the final visit at the end of the follow-up period.

Discrete variables are presented as absolute and relative numbers. For continuous variables, the Shapiro-Wilk test was performed to determine the normality of distribution. Depending on the results of the Shapiro-Wilk test, mean and SD or median with IQR were reported. For discrete variables, group comparisons were performed using χ^2 tests. Continuous variables were compared with either t-tests or Mann-Whitney U tests, according to the normal distribution assumption. Data are presented as boxplots or mean plots with error bars. A p value of 5% was determined as significant for all analyses. For the main analyses, we compared the CG with the IG using an intention-to-treat approach. The effect size for the Mann-Whitney U tests was calculated using rank-biserial correlation; for t-tests, Cohen's d was calculated. This study

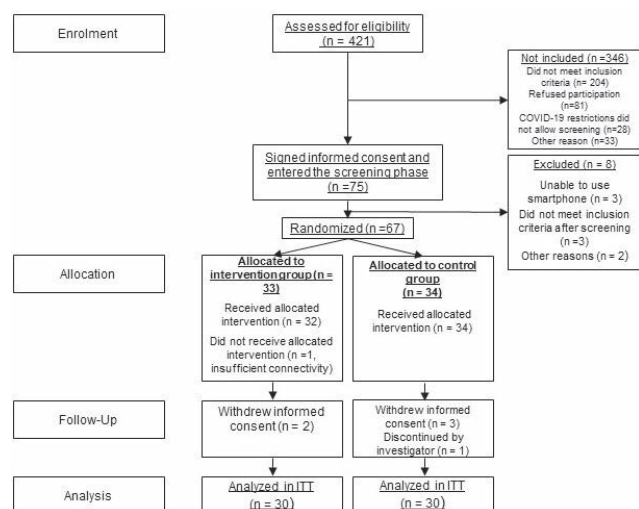


Figure 1 Consolidated Standards of Reporting Trials diagram. ITT, intention to treat.

was designed as a superiority study, and analyses were performed using the R V.4.1.1.

RESULTS

Recruitment and baseline characteristics

Overall, 421 subjects were screened for eligibility. The trial was conducted from July 2019 to June 2021. Enrolment was terminated after the planned number of participants completed the study (n=52). Figure 1 shows the protocol for screening, randomisation and follow-up. Table 1 shows the baseline demographics of the 67 randomised patients. The 67 participants with COPD had a mean age of 64 ± 8 years and, according to the pulmonary function testing, severe airflow obstruction with a mean FEV₁% predicted of $44\% \pm 16\%$. Comorbidities are illustrated in table 2, showing no group differences according to distribution.

Primary outcome

The main analysis showed a significant difference in the change in median steps from baseline to 6 months between the groups (IG -105.9 , IQR -1970.1 to 2105.8 , vs CG -1173.0 , IQR 3813.1 to -93.8 steps per day; $p=0.007$) (figure 2). The effect size was 0.402 (IQR 0.131 – 0.617).

The median number of daily steps at 6 months measured as an average value over 7 days was significantly higher in the IG (median steps and IQRs in the IG 5016.3 (2920.3 – $10\,206.5$) vs 3105.1 (606.4 – 4372.0), $p=0.014$) than in the CG (figure 3). The effect size was 0.370 (IQR 0.095 – 0.593).

At baseline and 3 months, the differences were not significant between the groups (baseline, IG 6361.4 (IQR 3401.2 – 8304.3) vs CG 5052.21 (IQR 3531.9 – 8999.1) steps per day, $p=0.760$; effect size, 0.024 (IQR -0.264 to 0.309); 3 months, IG 4661.1 (IQR 2538.4 – 7829.0) vs CG 3728.0 (IQR 1889.3 – 5773.4) steps per day, $p=0.199$; effect size, 0.168 (IQR -0.125 to 0.433) (figure 3).

Secondary outcomes

COPD Assessment Test

CAT scores decreased from baseline to 6 months in the IG (-1.4 point mean difference) but increased in the CG by 3.7 points ($p=0.02$) (figure 4 and table 3).

Chronic Respiratory Disease Questionnaire

Significant differences were found between the IG and CG for the CRQ domains of dyspnoea and fatigue. The domains of emotional function and mastery, as well as the CRQ total score, did not show significant differences between groups (table 3).

Hospital Anxiety and Depression Scale

While Hospital Anxiety and Depression Scale–Depression Subscale (HADS- D) did not change significantly over the study pe-

Table 1 Demographic characteristics of the study population

Characteristics	Overall n=67	IG n=33	CG n=34
Age (years), mean (SD)	64.3 (7.7)	66.1 (6.8)	62.7 (8.2)
Sex (female), n (%)	33 (49.3)	16 (48.5)	17 (50.0)
BMI (kg/m ²), mean (SD)	24.4 (5.1)	25.0 (4.7)	23.8 (5.6)
Current smoker, n (%)	8 (11.9)	3 (9.1)	5 (14.7)
Smoking in the past, n (%)	58 (86.6)	30 (90.9)	28 (82.4)
Never smoker, n (%)	1 (1.5)	0 (0.0)	1 (2.9)
Exacerbation in the last 12 months, n (%)	53 (79.1)	29 (87.9)	24 (70.6)
Number of exacerbations treated as outpatient in the past 12 months, mean (SD)	1.19 (1.14)	1.19 (1.33)	1.19 (0.87)
Number of exacerbations treated as inpatient in the past 12 months, mean (SD)	1.08 (1.23)	1.21 (1.50)	0.91 (0.79)
Long-term oxygen therapy, n (%)	40 (59.7)	18 (54.5)	22 (64.7)
FEV ₁ (L) (mean (SD))	1.27 (0.50)	1.31 (0.53)	1.23 (0.46)
FEV ₁ % predicted (mean (SD))	44.0 (16.2)	45.5 (14.5)	42.6 (17.8)
FEV ₁ % FVC, mean (SD)	0.52 (0.14)	0.54 (0.14)	0.50 (0.15)
FVC% predicted, mean (SD)	64.8 (18.4)	63.9 (17.9)	65.7 (19.2)
CAT (points), mean (SD)	16.3 (7.09)	16.5 (7.2)	16.0 (7.1)
GOLD stage II, n (%)	20 (29.9)	10 (30.3)	10 (29.4)
GOLD stage III, n (%)	29 (43.3)	17 (51.5)	12 (35.3)
GOLD stage IV, n (%)	18 (26.9)	6 (18.2)	12 (35.3)

BMI, body mass index; CAT, COPD Assessment Test; CG, control group; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Obstructive Lung Disease; IG, intervention group.

riod for the IG, the scores significantly increased for the CG (IG 4.20 (± 2.95) vs CG 6.55 (± 5.08), $p=0.033$) (figure 5). Group differences for the Hospital Anxiety and Depression Scale–Anxiety Subscale (HADS- A) and the total scores were not significant at 6 months (table 3).

Sit-to-Stand Test

At baseline, no significant difference in the number of STST repetitions was observed. After 3 months, participants in the IG performed a significantly higher number of repetitions, and after 6 months, no significant difference was noted in the number of STST repetitions (figure 6 and table 3).

Sleep parameters

Regarding sleep duration and sleep efficiency, no differences were found for both the CG and IG at any time (table 3).

App usage and adherence

The app usage for the IG is reported in line with adherence to definitions previously reported and listed in table 4.¹⁴ A prespecified optimal usage rate of four different types of content, on four different days per week, was achieved by 36% of the participants. Using the prespecified adherence definition (use of the application at least four times a week for at least 70% of the weeks during the

Table 2 Comorbidities of the study population

Comorbidities	Overall n=67	IG n=33	CG n=34
Cardiac comorbidity, n (%)	39 (58.2)	20 (60.6)	19 (55.9)
Neurological comorbidity, n (%)	9 (13.4)	6 (18.2)	3 (8.8)
Metabolic comorbidity, n (%)	18 (27.3)	11 (33.3)	7 (21.2)
Musculoskeletal comorbidity, n (%)	28 (41.8)	17 (51.5)	11 (32.4)
Psychiatric comorbidity, n (%)	16 (23.9)	8 (24.2)	8 (23.5)
Other comorbidities, n (%)	26 (38.8)	17 (51.5)	9 (26.5)
History of lung surgery, n (%)	3 (4.5)	1 (3.0)	2 (5.9)

CG, control group; IG, intervention group.

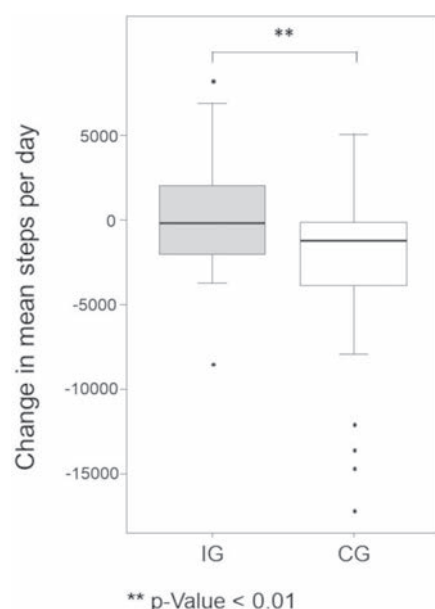


Figure 2 Changes in steps per day from baseline to 6 months. P value was obtained from the Mann-Whitney U test. CG, control group; IG, intervention group. ** $P < 0.01$.

study), 13 participants (43%) in the IG complied fully with the app usage suggestions ('frequent app user'). As a sensitivity analysis, we reanalysed this subgroup of patients and found an even greater difference when compared with controls regarding the primary outcome (change in steps from baseline in the IG 1092.1 (−1036.3 to 2317.9) and in the CG −1173.0 (−3813.1 to −93.8), $p = 0.006$). The results of the subgroup frequent app user are provided in online supplemental table S7). A visual representation of the participants' app usage is shown in figure 7.

Of the 30 participants, 29 (96.6%) completed the study, indicating that they were satisfied with the study app after using it. Ten (34.5%) participants rated it as 'okay', and 18 (62.1 %) rated it as 'very satisfactory'. All participants would recommend the app to other patients with COPD. There were no differences in safety endpoints. More detailed information regarding safety endpoints is provided in the online supplemental material.

DISCUSSION

The study investigated the effects of a digital-based post-PR programme provided via a smartphone app to maintain the positive results of PR as long as possible and to encourage patients to adopt a more active lifestyle. The results demonstrate that the maintenance of PA and a significant increase in HRQoL, up to 6 months after completing PR, were possible by using a mobile app

for self-management of COPD. To our knowledge, this study is the first RCT to demonstrate the maintenance of PA after inpatient PR using a digital structured programme. In addition, differences in favour of the IG could be found in all observed endpoints of the study (except HADS-A) after 6 months, exceeding the minimal clinically important differences (online supplemental material). These positive app results are particularly impressive because the CG received the usual postrehabilitation recommendations rather than no intervention. In addition to the application providing potential benefit of maintenance after participating in PR, it may provide benefit of increasing the uptake of digital delivery of PR overall.

PR has been demonstrated to significantly and reliably improve HRQoL and exercise capacity. However, the long-term effects on PA are moderate. Given its resource-intensive and costly nature, consolidation and maintenance of PR-induced benefits, especially in maintaining PA, remain a challenge across modes of delivery and healthcare systems. Structured exercise programmes aimed to improve the maintenance of benefits after PR showed mixed results when assessing exercise tolerance, HRQoL and PA.²⁸

Additionally, the findings of the current study are of relevance because PA is an important outcome. Previous studies on this topic have shown ambivalent results, and most studies have focused on physical performance as the primary endpoint.^{7,8} Since a higher exercise capacity does not necessarily lead to higher PA,^{7,29} it is of particular interest to evaluate the effects of a postrehabilitation programme on PA. Physical inactivity is a potential modifiable risk factor and should be clinically assessed as a vital sign of a patients' general physical condition prior to any exercise-based intervention.³⁰

In this study, training on the use of the study equipment occurred during rehabilitation (four sessions, each of 20 min duration). When reduced to pure training with the app, the effort would be significantly lower, and a cost-effective and feasible application would be conceivable in the outpatient area. However, the extent to which a reduction in training times has an influence on adherence to the training app cannot be estimated.

Barriers to referral, uptake and completion of PR are well documented and linked with organisational, practitioner and patient-related factors.³¹ However, the extent to which the use of a training app can close a gap here must certainly be evaluated in further studies. Findings from studies of maintenance programmes following PR are heterogeneous, especially regarding supervision frequency. A recently published Cochrane review including 21 studies with 1799 patients with COPD suggested that supervised maintenance programmes for patients with COPD after PR may improve HRQoL and could possibly improve exercise capacity at 6–12 months. The strength of the evidence was assessed as limited. The authors concluded that the optimal frequency of supervision and mode for supervised maintenance programmes are still un-

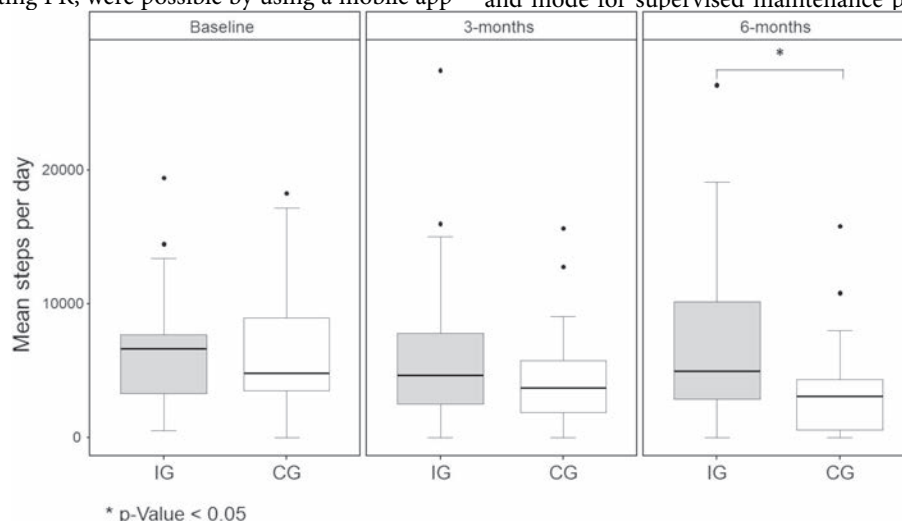


Figure 3 Steps per day at baseline and 3 and 6 months for the IG and the CG. P value obtained from the Mann-Whitney U test. CG, control group; IG, intervention group. * $P < 0.05$.

Table 3 Results of secondary endpoints for the IG and CG

	Baseline			3 months			6 months					
	IG	CG	P value	Effect size (95% CI)	IG	CG	P value	Effect size (95% CI)	IG	CG	P value	Effect size (95% CI)
CAT points	16.53 (7.15)	16.00 (7.12)	0.773	0.075 (−0.432 to 0.581)	15.53 (8.26)	18.70 (6.71)	0.109	−0.421 (−0.931 to 0.093)	15.13 (8.58)	19.72 (6.42)	0.024	−0.605 (−1.124 to 0.080)
STST repetitions	19.07 (5.77)	16.87 (7.07)	0.196	0.341 (0.175 to 0.853)	22.87 (8.00)	16.83 (7.64)	0.004	0.771 (0.243 to 1.293)	22.66 (7.23)	19.45 (9.09)	0.143	0.390 (−0.131 to 0.908)
CRQ domains												
Dyspnoea points	4.54 (1.45)	4.48 (1.19)	0.881	0.039 (−0.467 to 0.545)	4.51 (1.68)	3.96 (1.40)	0.170	0.359 (−0.153 to 0.868)	4.54 (1.65)	3.69 (1.31)	0.033	0.570 (0.047 to 1.089)
Fatigue points	4.60 (1.22)	4.68 (1.31)	0.820	−0.059 (−0.565 to 0.447)	4.31 (1.36)	3.74 (1.13)	0.085	0.453 (−0.062 to 0.963)	4.50 (1.28)	3.72 (1.36)	0.028	0.586 (0.062 to 1.105)
Emotional function points	5.40 (1.07)	5.14 (0.97)	0.325	0.256 (−0.253 to 0.763)	4.90 (1.31)	4.41 (1.32)	0.161	0.367 (−0.145 to 0.875)	4.92 (1.27)	4.54 (1.40)	0.283	0.282 (−0.232 to 0.794)
Mastery points	5.27 (1.23)	4.97 (1.27)	0.369	0.234 (−0.275 to 0.740)	5.18 (1.44)	4.63 (1.64)	0.180	0.351 (−0.161 to 0.859)	5.08 (1.50)	4.48 (1.51)	0.131	0.399 (−0.118 to 0.913)
Total CRQ points	4.95 (1.07)	4.82 (0.97)	0.618	0.129 (−0.378 to 0.636)	4.72 (1.31)	4.19 (1.18)	0.102	0.429 (0.085 to 0.940)	4.76 (1.30)	4.11 (1.26)	0.056	0.508 (−0.013 to 1.024)
Feeling thermometer degrees	61.57 (19)	61.57 (17)	1.000	0.000 (−0.506 to 0.506)	65.0 (20)	63.50 (20)	0.772	0.075 (−0.431 to 0.581)	66.43 (18)	58.93 (21)	0.147	0.383 (−0.134 to 0.896)
HADS-A points	4.10 (3.33)	4.10 (3.50)	1.000	0.000 (−0.506 to 0.506)	4.60 (3.74)	6.10 (4.16)	0.147	−0.380 (−0.889 to 0.133)	4.43 (3.50)	5.34 (4.19)	0.368	−0.236 (−0.748 to 0.277)
HADS-D points	4.23 (2.90)	4.23 (3.69)	1.000	0.000 (−0.506 to 0.506)	4.50 (2.74)	6.03 (4.41)	0.111	−0.418 (−0.928 to 0.095)	4.20 (2.95)	6.55 (5.08)	0.033	−0.569 (−1.087 to −0.046)
HADS total points	8.33 (5.60)	8.33 (6.47)	1.000	0.000 (−0.506 to 0.506)	8.33 (5.60)	8.33 (6.47)	1.000	0.000 [−0.506 to 0.506]	8.33 (5.60)	8.33 (6.47)	1.000	0.000 (−0.506 to 0.506)
Duration of sleep (hours)	7.61 (1.36)	7.73 (1.08)	0.703	−0.102 (0.621 to 0.418)	7.32 (1.28)	7.49 (1.89)	0.704	−0.105 (−0.644 to 0.434)	7.60 (1.31)	7.13 (1.69)	0.294	0.311 (−0.269 to 0.888)
Sleep efficiency (%)	91.71 (3.20)	90.84 (3.33)	0.321	0.265 (−0.257 to 0.786)	92.39 (2.37)	90.97 (2.73)	0.048	0.555 (0.004 to 1.102)	91.95 (2.28)	90.75 (2.93)	0.120	0.465 (−0.120 to 1.046)
Data are presented as mean and SD, and all p values were obtained from the t-tests.												
CAT, COPD Assessment Test; CG, control group; CRQ, Chronic Respiratory Disease Questionnaire; HADS, Hospital Anxiety and Depression Scale; HADS-A, Hospital Anxiety and Depression Scale–Anxiety Subscale; HADS-D, Hospital Anxiety and Depression Scale–Depression Subscale; IG, intervention group; STST, Sit-to-Stand Test.												

Data are presented as mean and SD, and all p values were obtained from the t-tests.

CAT, COPD Assessment Test; CG, control group; CRQ, Chronic Respiratory Disease Questionnaire; HADS, Hospital Anxiety and Depression Scale–Anxiety Subscale; HADS-D, Hospital Anxiety and Depression Scale–Depression Subscale; IG, intervention group; STST, Sit-to-Stand Test.

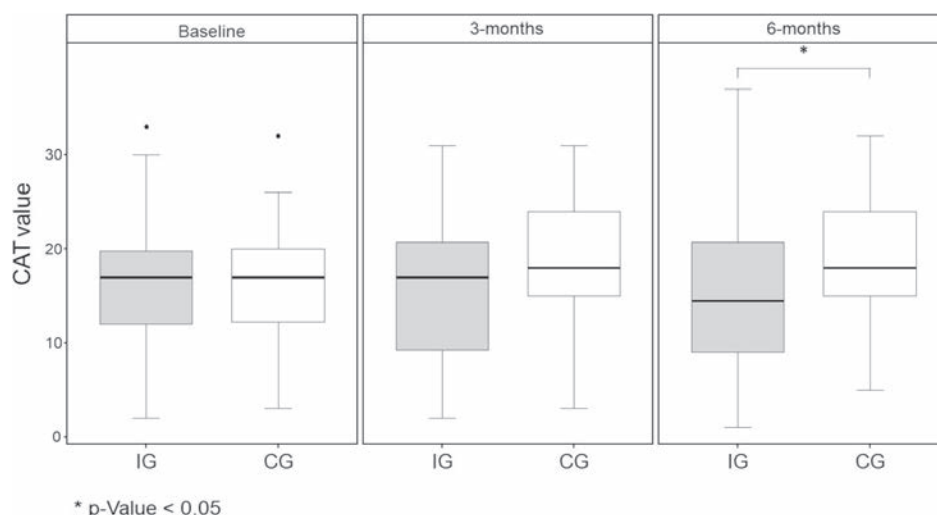


Figure 4 Results of the CAT for the IG and the CG. P value was obtained from the t-test. CAT, COPD Assessment Test; CG, control group; IG, intervention group. *P<0.05.

clear.³² However, these studies also predominantly examined only the effects on the participants' physical performance and not the consequences in terms of PA. Interestingly, no significant changes between CG and IG were seen in the 3-month assessment. We suppose this to be the usual duration that PR effects are measurable. By the extended observation period of 6 months, significant differences between the groups could be seen. Our results confirm the experience of the ATS guidelines, stating that the benefits of PR in the absence of any main-tenance strategy appeared to diminish over 6–12 months.³ Another study tried to demonstrate the effects of an mHealth intervention to improve or maintain PA in patients with COPD after PR. However, no differences were observed in PA, functional exercise capacity, HRQoL outcomes or body mass index in patients with COPD using a consumer smartphone-based mHealth intervention.³³ The discrepancies between outcomes of the previous study and the current study might be caused by the different settings, as patients in the previous study were enrolled until half a year after outpatient PR, and the different inclusion and exclusion criteria. In addition, differences between study interventions might have played a role.

Other disease-relevant outcomes such as the CAT, HRQoL measured by the dyspnoea and fatigue domains of the CRQ, and data on the mood of the patients assessed with the HADS-D showed a significant improvement in the IG compared with CG. Regarding the STST, a clinically and statistically significant difference was observed at 3 months, while no significant difference was noted at 6 months, which may be caused by the fact that the study was not sufficiently powered to detect such a change in the STST. These findings are in line with the effects observed in a re-

spective pilot study of the same application, showing at least a significant improvement in the CAT score and the identical CRQ domains from baseline to the end of the observational period.¹⁶ Our results support the findings of North et al, who had previously reported non-inferiority of a mHealth intervention to outpatient face-to-face PR on changes in functional exercise capacity and HrQoL in patients with COPD meeting referral criteria to PR.¹³ In a recent study among patients with severe COPD, tele-rehabilitation (delivered through providers instead of an app) also yielded equal results to face-to-face PR.³⁴ Of note, all participants in our study were included following a comprehensive rehabilitation, assuming that the patients were in their best possible condition with little potential for further improvements.

Another pilot study investigated the same intervention as Crooks et al in inpatients with COPD following an exacerbation and found clinically relevant effects on HRQoL and the incidence of exacerbations.¹⁴ This study also reported an effect of a digital health intervention on PA, HRQoL and functional exercise capacity. The findings suggest that inpatient populations either are especially prone to profit from these interventions or reflect the well-documented effect of PR following exacerbations, as the majority of the participants of this study also had a history of a recent exacerbation.³⁵

Notably, no significant difference was found between the groups with respect to the number of recorded exacerbations or adverse events (AEs). The intervention had a positive safety profile with a comparable incidence and distribution of AEs across the groups. These results are in line with the findings of the aforementioned Cochrane review showing that supervised maintenance pro-

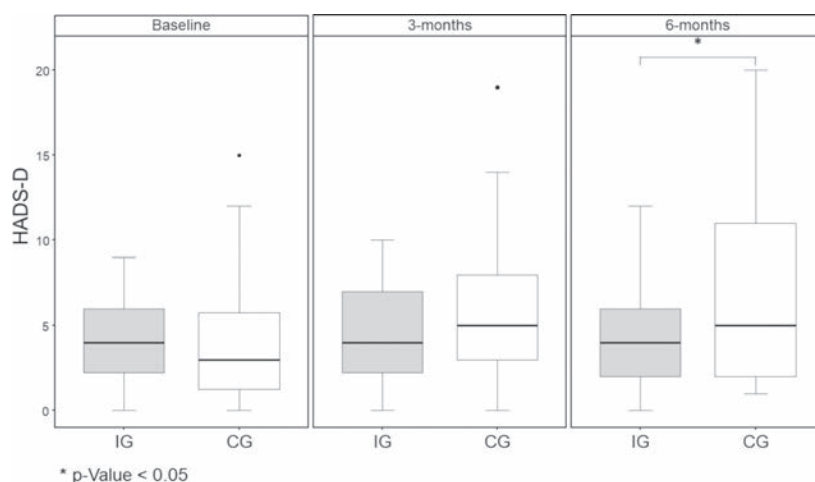


Figure 5 Results of the HADS-D for the IG and the CG. P value was obtained from the t-test. CG, control group; HADS-D, Hospital Anxiety and Depression Scale–Depression Subscale; IG, intervention group. *P<0.05.

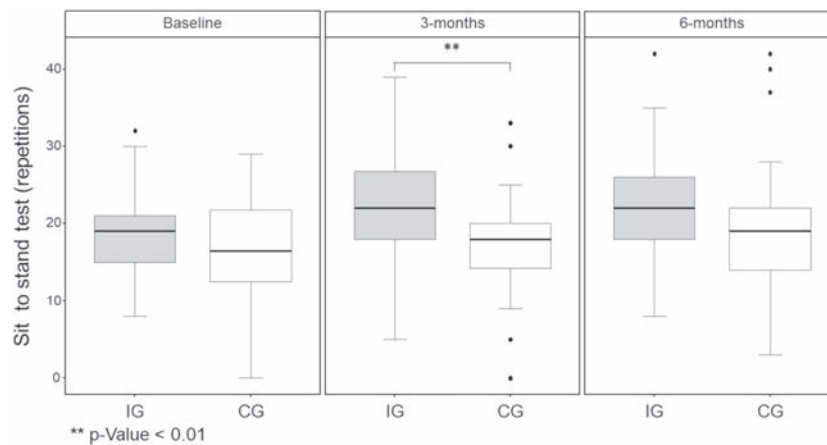


Figure 6 Results of the 1 min Sit-to-Stand Test for the IG and the CG. P value was obtained from the t-test. CG, control group; IG, intervention group. **P<0.01.

grammes for patients with COPD after PR are not associated with increased AEs.³³

However, it is still unknown which patients, in terms of disease progression or demographic properties, benefit the most from digital health apps for PR. Another recent pilot study investigated the use of an mHealth app in a collective of newly diagnosed, mild and moderately affected patients with COPD, but observed no clinically or statistically relevant effect on HRQoL, even if the study was powered comparably to the current study.¹⁴ However, in both studies, the patient's baseline symptoms and demographics were comparable. Crooks et al showed that changes in CAT during the study period were more favourable with higher app usage. In the

current study, results of the frequent app user subgroup indicated that increased usage creates greater advantages. Furthermore, this subgroup even increased their PA rather than just maintained it. Hence, it seems that increasing adherence motivation might be a key to achieving favourable results in mHealth app usage by patients with COPD. The finding that uptake of and adherence to digital health intervention is indeed a challenge in patients with COPD was also confirmed.³⁶ It is quite conceivable that the use of the app can be beneficial even without prior rehabilitation. This is the subject of the current study and will be reported in the future.

App usage in the current study was sustained over the observational period in most participants in the IG. In this context, previous trials of digital health interventions for PR have repeatedly shown that adherence to the intervention is crucial for favourable outcomes, but adherence is difficult. Previous studies have reported that 28% of patients do not use an app after 1 month (40% at 3 months).^{12,13} Long-term adherence of >3 months for digital interventions has only been assessed by a few trials but seems to be a remarkable challenge in those studies with below 20% of participants completing the 6-month programme.³⁷ The long-term usage rates in the current study suggest acceptable patient engagement throughout the observational period.

The observational period of our study suggests that using a digital health tool maintains PA after PR during an observational period of 6 months. This exceeds the observational periods of previous studies that have investigated the effect of digital tools on self-management in patients with COPD, which ranges mostly from 6 to 12 weeks.² Implementing a long observational period is important since continued use and sustained demonstration

Table 4 Usage of the COPD app in the intervention group

	n (%)
Total use definitions	
Activating the app and at least one activity	29 (97)
Training on the app on at least 30 days	26 (87)
Training on the app on at least 60 days	24 (80)
Training on the app on at least 90 days	20 (67)
Training on the app on at least 120 days	13 (43)
Sustained use definitions	
An activity in the app in at least 50% of trial weeks (%)	79
An activity in the app in at least 75% of trial weeks (%)	61
Number of active days in the final week of the study (SD)	3.51 (2.71)
app, smartphone application.	

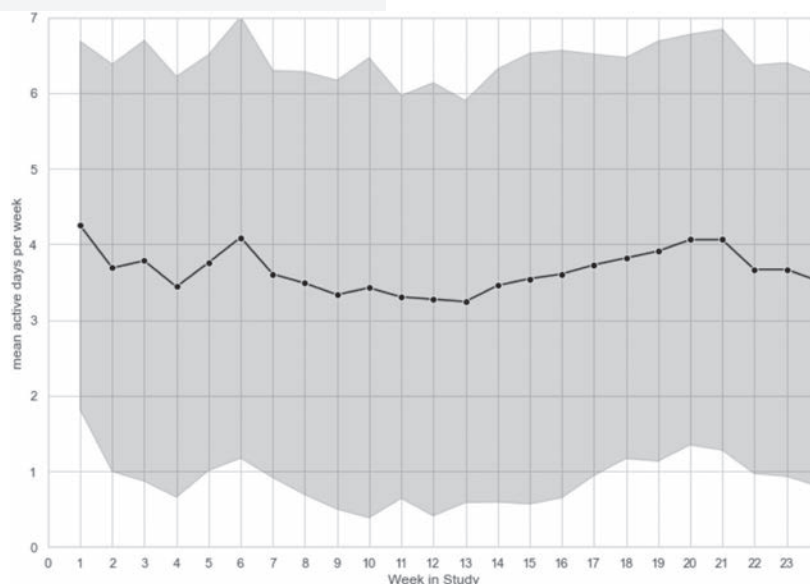


Figure 7 Usage rates per week during the observational period. Mean values are indicated by the black line and dots; SDs are indicated by grey bars.

of positive clinical outcomes of digital health tools have been described as a problem that needs to be addressed.³⁶

This study has some limitations. First, the sample size was small. However, the statistical considerations according to the primary endpoint assumed a total sample size of 52 patients. In this study, the results of 60 patients were finally analysed, allowing for appropriate interpretation of the primary endpoint. However, in consequence, additional studies with larger sample sizes will help elucidate the effects of the intervention in broader settings. Second, more than three other sites were asked to participate; however, due to several reasons (eg, no sufficient inpatient PR case load in COPD and no adequate research infrastructure), only two sites were eligible. Third, the results of this study may not be generalisable to a broader population of patients with COPD. According to the aim and the defined inclusion criteria of the study, a preselection of patients in the COPD rehabilitation population was necessary, showing sufficient verification in mobile technology. Hence, even though the authors tried to mitigate this by offering smartphones and a corresponding education as part of the intervention, the study was mainly limited to smartphone users.

Fourth, the nature of the intervention made blinding of the study participants and study staff impossible. Although this problem is commonplace in rehabilitation trials, the lack of blinding is a limitation. To reduce the risk of bias, other procedures such as proper allocation concealment were implemented to ensure rigour and reproducibility. Selection bias may have been introduced in the study through the screening criteria which might select for participants compliant with the study intervention; this may have an effect on adherence and patient engagement. Fifth, while the study showed significant benefits of the intervention over an observational period of 6 months, the effects during a longer observational period like 12 months have not been assessed.

CONCLUSIONS

Digital interventions are an interesting option to support the management of chronic conditions such as COPD. For these digital interventions to be meaningful, integration into the existing healthcare landscape is paramount, and it may provide benefit of increasing the uptake of digital delivery of PR overall. This study reveals how a digital intervention can be used to supplement existing care by closing gaps in the existing healthcare landscape. However, to make a general recommendation on the benefit of an app as a maintenance programme after PR in patients with COPD, further studies are required.

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Contributors MS was the principal investigator for Switzerland and supervised the study, PR programme and data collection; ARK was the principal investigator for Germany. MS, TB, SH, PK, B, A, MP, SS, RG, II, TS, DL and ARK contributed to the study concept and design, as well as in the data collection. MS and SH wrote the first draft of the manuscript, which was critically reviewed by RG, PK, B, SS, ARK, WW, II, and TS. BU contributed for the statistical analysis. All authors participated in various steps in the study, edited the manuscript and gave their approval for submission. MS is the guarantor of the article.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Swiss Ethics Committee (BASEC 2019-00766) and the German Ethics Committee of the University of Marburg (number 96/19). The participants gave informed consent to participate in the study before taking part. The investigation conformed to the principles outlined in the Declaration of Helsinki.

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Data availability statement Deidentified and aggregated participant data are available from the corresponding author on reasonable request, subject to approval by an independent ethics committee.

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ARTIGO ORIGINAL

Impacto do tempo até ao tratamento na sobrevivência de pacientes com cancro do pulmão de células não-pequenas nos Países Baixos: um estudo de coorte nacional observacional

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RESUMO

Contexto A suposição de que um tratamento mais rápido melhora a sobrevivência do cancro do pulmão de células não-pequenas (NSCLC) ainda não foi provada. Estudámos a relação entre o tempo até ao tratamento e a sobrevivência em pacientes com NSCLC em estado avançado numa grande coorte multicêntrica nacional retrospectiva. Além disso, identificámos fatores associados ao atraso.

Método Seleccionámos 10 306 pacientes, diagnosticados e tratados entre 2014 e 2019 com NSCLC clínico de estadio III e IV do Registo de Cancro dos Países Baixos, que inclui dados nacionais de 109 hospitais neerlandeses. As associações entre a sobrevivência e o tempo até ao tratamento foram testadas com análise de regressão de risco proporcional de Cox. O tempo até ao tratamento foi ajustado a múltiplas covariáveis, incluindo procedimentos de diagnóstico e tipo de terapia. Os fatores associados ao atraso foram identificados através de regressão logística multinível.

Resultados O risco de morte diminuiu significativamente com um tempo até ao tratamento mais longo nos pacientes em estadio III, que receberam apenas radioterapia (HR ajustado, aHR >21 dias: 0,59 (IC 95% 0,48 a 0,73)) ou qualquer tipo de tratamento sistémico (aHR >49 dias: 0,72 (IC 95% 0,56 a 0,91)) e pacientes de estadio IV, que receberam quimioterapia e/ou imunoterapia (aHR >21 dias: 0,81 (IC 95% 0,73 a 0,88)). Não foi detetada qualquer associação significativa no caso dos pacientes em estadio III tratados com quimiorradioterapia e os pacientes em estadio IV tratados com terapêutica orientada. Os procedimentos de diagnóstico mais complexo atrasam frequentemente o tratamento.

Conclusão Embora, em geral, seja importante começar o tratamento assim que possível, o nosso estudo não encontrou quaisquer provas de que um início mais rápido do tratamento melhora o resultado em pacientes com NSCLC em estadio avançado. O benefício do tratamento urgente é, provavelmente, confundido com características dos pacientes e do tumor não medidas e a urgência clínica que dita os calendários de tratamento. O tempo até ao tratamento e o seu impacto devem ser avaliados continuamente à medida que as estratégias terapêuticas continuam a evoluir e a melhorar.

INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer diagnosis and has an overall 5-year survival rate of only 24%.^{1,2} Most patients have locally advanced or metastatic disease at the time of presentation, which is likely to be a result of the long time before symptom onset.³ In recent years, the arrival of immunotherapy, targeted therapy and combined chemioimmunotherapy improved prognosis of advanced NSCLC.^{4–6} Molecular diagnostics have become part of the clinical routine to identify patients who may benefit from targeted therapy or immunotherapy.⁷

Key messages

What is already known on this topic

► Previous literature indicates a complex association between time-to-treatment and survival for advanced non-small cell lung cancer. We studied this relation in a Western country with equal access to healthcare and identified factors associated with longer waiting times.

What this study adds

► The ‘sicker-quicker’ effect is most likely caused by unmeasured confounders relating to patient and tumour characteristics rather than factors related to the hospital infrastructure. Also effectiveness of therapy and presence of an actionable mutation seem to surround this paradox.

How this study might affect research, practice or policy

► An ongoing evaluation of time-to-treatment and its impact on outcomes will be needed as therapeutic strategies continue to evolve and improve.

Although these tests can improve patient outcomes, the diagnostic turnaround time may result in prolonged time-to-treatment.⁸ Delays in the diagnostic work-up are conceived as a medical risk due to the aggressiveness of advanced NSCLC.^{9,10}

In the Netherlands, guidelines and several medical institutions have published timelines to establish standards for timely care of patients with known or suspected (lung) cancer varying from 30 to 49 days.^{11–14} Variations in these recommendations mark a national heterogeneity that is reflected by a Dutch retrospective cohort study.¹⁵ In this study, substantial differences in time-to-treatment on hospital-level were reported for advanced NSCLC with medians ranging from 17 to 68 days.¹⁵

The assumption is that prompt diagnosis and treatment lead to better patient outcomes. However, not all evidence supports this: previous literature frequently found shorter time-intervals to be associated with poorer survival for advanced NSCLC.^{16–21} The evidence for benefit of shorter time intervals seems stronger for surgical early-stage NSCLC patients.²² The paradoxical findings for advanced stages indicate a complex association between time-to-treatment and survival.

We suspect that this association is not only influenced by patient and tumour characteristics but also determined by hospital infrastructure such as the turnaround time of diagnostic tests.²³

Therefore, the objective of this study was twofold: First we examined the association between time-to-treatment and overall survival (OS) in a large nationwide retrospective cohort. Second, we identified factors associated with a longer time-to-treatment.

METHODS

Source

Information regarding clinical stage III and IV NSCLC patients from 2014 to 2019 was retrieved from The Netherlands Cancer Registry (NCR), after approval by the Privacy Review Board. In accordance with the regulations of the Central Committee on Research involving Human Subjects, this observational retrospective cohort study does not require approval from an ethic committee in the Netherlands. The NCR collects data on all cancer patients diagnosed in the Netherlands, based on notification of newly diagnosed malignancies by the national automated pathological archive and hospital discharge diagnoses. The data had been collected in 109 hospitals and includes information on patient and tumour characteristics, diagnostics and treatment and is extracted routinely from the medical records by specially trained NCR personnel. Tumour staging was recorded according to the seventh and eighth edition of the TNM (T=tumor, N=node, M=metastasis) classification.²⁴ Information on vital status and date of death is updated annually using a computerised link with the national civil registry. Information on performance status is registered since 2015, and information on comorbidities, lung function tests and smoking status is not available.

Patient selection

From 2014 to 2019, the NCR recorded 58 312 patients diagnosed with clinical stage III or IV NSCLC. The following cases were considered eligible: age >18 years and patients who received tumour-directed treatment (stage III: chemoradiotherapy, radiotherapy or systemic therapy; stage IV: systemic therapy). We excluded patients with a time-to-treatment of <0 days or >180 days (<1%) and missing information on time-to-treatment. Negative time intervals were for example seen in patients who have visited pulmonologists in multiple hospitals. A maximum cut-off value of 180 days was used as larger time intervals were mostly caused by patients' preferences. Because the Dutch Lung Cancer Guidelines allow other lead times for patients with an indication for mediastinoscopy (49 days), these patients were excluded.¹⁴ Additionally, we excluded patients who entered the clinical pathway differently (eg, via the emergency department instead of an outpatient appointment) because these patients represent a group with symptomatic disease leading to different choices and

possibilities in the diagnostic pathway. These patients often suffer from other primary health problems or show acute lung cancer-related symptoms. This may affect the relation between time-to-treatment and survival differently from those patients who enter the diagnostic pathway via an outpatient visit with a pulmonologist. After exclusion, 10 306 patients were included for analysis (figure 1). All patients were followed from the index to death or February 2020.

Study variables

Our main variable of interest was time-to-treatment, calculated in days from first outpatient visit with a pulmonologist for suspected lung cancer till start of treatment.¹⁴

We have discussed all variables of the NCR dataset thoroughly with medical experts involved in lung cancer care (eg, pulmonologist, radiologists). For multivariable analysis, we selected those variables that could affect OS and timing of treatment: age was grouped in 18–60, 61–70, 71–80 and 80+ years. History of cancer was registered if the patient was diagnosed with another type of cancer 5 years before NSCLC. Socioeconomic status was provided by the Netherlands Institute for Social Research at an aggregated level for each postal code and determined from the average income, proportions with low income, low educational level, and unemployment, and categorised as low (1–4), intermediate (5–7) and high (8–10). Year of diagnosis was grouped in 2014, 2015–2016 and 2017+. Since the impact of age, socioeconomic status and year of diagnosis was not linear, these factors were included as categorical variables in the model. We based categorisation of year of diagnosis on the development of (new) therapeutic strategies and agents (ie, introduction of immunotherapy in 2015 for stage IV) and the introduction of the eighth version of the TNM classification in 2017. The well-being of the patient was indicated by the Eastern Cooperative Oncology Group Performance Status (ECOG PS) and the Karnofsky scale (10–100). Karnofsky scores were converted to ECOG PS and grouped in 0, 1, 2, 3–4 and unknown.²⁵ The histology of the tumour was grouped by type according to the third edition of the International Classification of Disease for Oncology: adenocarcinoma, squamous cell carcinoma, large cell carcinoma and clinical diagnosis wherever pathological confirmation was not possible. Distant metastasis were categorised in M1a and M1b/M1c. Treatment with chemoradiotherapy included concurrent and sequential, whereas concurrent was defined as chemotherapy and radiotherapy starting within 30 days from each other and sequential as chemotherapy and radiotherapy starting between 30 and 90 days from each other.²⁶ Systemic therapy comprised of chemotherapy, immunotherapy, targeted and combined chemoimmunotherapy while radiotherapy covered stereotactic body radiation therapy and radiation focused on primary tumour and, on metastasis.

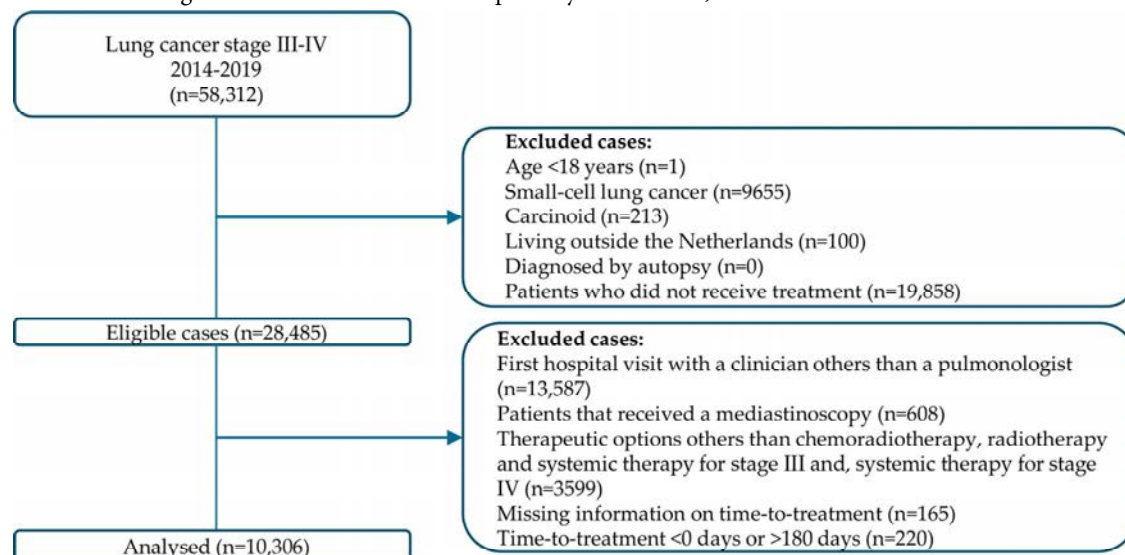


Figure 1 Study flow chart.

Table 1 Patients' demographic and clinical characteristics by stage and type of therapy for advanced NSCLC who were diagnosed and treated between 2014–2019 in the Netherlands

Characteristics	Total cohort advanced NSCLC (n=10 306)				
	Total, N*	Stage III ChemoRT (n=2772) Patients, %	Stage III RT (n=1359) Patients, %	Stage III ST (n=907) Patients, %	Stage IV ST (n=5268) Patients, %
Age (years)					
18–60	2655	792 (29)	220 (16)	189 (21)	1454 (28)
61–70	3928	1125 (40)	391 (29)	353 (39)	2059 (39)
71–80	3062	754 (27)	482 (35)	294 (32)	1532 (29)
80+	661	101 (4)	266 (20)	71 (8)	223 (4)
Gender					
Male	5878	1600 (58)	861 (63)	513 (57)	2904 (55)
Female	4428	1172 (42)	498 (37)	394 (43)	2364 (45)
Socioeconomic status					
Low	5864	1615 (58)	756 (56)	524 (58)	2969 (56)
Intermediate	2422	658 (24)	315 (23)	228 (25)	1221 (23)
High	2020	499 (18)	288 (21)	155 (17)	1078 (21)
History of other cancer					
Yes	748	207 (7)	146 (11)	86 (9)	309 (6)
No	9558	2565 (93)	1213 (89)	821 (91)	4959 (94)
Year of diagnosis					
2014	1349	432 (16)	177 (13)	128 (14)	612 (12)
2015–2016	3410	935 (34)	486 (36)	297 (33)	1692 (32)
2017–2019	5547	1405 (50)	696 (51)	482 (53)	2964 (56)
Performance status†					
0	2659	870 (31)	226 (17)	213 (23)	1350 (26)
1	3159	858 (31)	338 (25)	272 (30)	1691 (32)
2	767	116 (5)	211 (16)	69 (8)	371 (7)
3+4	192	16 (1)	91 (6)	11 (1)	74 (1)
Unknown	3529	912 (32)	493 (36)	342 (38)	1782 (34)
Histology					
Adenocarcinoma	5696	1129 (41)	434 (32)	414 (46)	3719 (71)
Squamous cell	2742	1100 (40)	572 (42)	313 (35)	757 (14)
Large cell	1580	506 (19)	191 (14)	156 (16)	727 (14)
Other‡	288	37 (0)	162 (12)	24 (3)	65 (1)
EUS					
Yes	1294	475 (17)	174 (13)	137 (15)	508 (10)
No	9012	2297 (83)	1185 (87)	770 (85)	4760 (90)
EBUS					
Yes	3284	1452 (52)	562 (41)	355 (39)	915 (17)
No	7022	1320 (48)	797 (59)	552 (61)	4353 (83)
Surgical exploration					
Yes	87	27 (1)	8 (1)	13 (1)	39 (1)
No	10219	2745 (99)	1351 (99)	894 (99)	5229 (99)
Transthoracic biopsy§					
Yes	808	174 (6)	111 (8)	81 (9)	442 (8)
No	4739	1231 (44)	585 (43)	401 (44)	2522 (48)
Unknown	4759	1367 (50)	663 (49)	425 (47)	2304 (44)
Distant metastasis (stage cM)¶					
M1a	1799	-	-	-	1799 (34)
M1b	2005				2005 (38)
M1c	1464				1464 (28)

*Percentages were horizontally calculated for each category and the numbers in the column total represent 100%.

†Registered since 2015.

‡Other: Rare histological subtypes, clinical diagnosis.

§Registered since 2017.

¶Located in bone, pleura, lung, adrenal gland, brain, liver, other.

ChemoRT, chemoradiotherapy; EBUS, Endo Bronchial Ultrasound; EUS, endoscopic ultrasound; NSCLC, non-small cell lung cancer; RT, radiotherapy; ST, systemic therapy.

Analysis

Statistical analyses were conducted in SAS, V.9.4 (SAS Institute). Descriptive statistics were presented as proportions of patients per stage and therapeutic strategy (table 1). Stratification according to

stage was consistently applied in further statistical analysis where the significance level was set at a $p < 0.05$. The data were also stratified for type of therapy in the survival analysis. Primary outcomes were OS in relation to time-to-treatment and, factors associated

Table 2 Multivariable Cox regression clinical stage III and IV NSCLC; (aHR (95% CI)) for mortality associated with time-to-treatment

Time-to-treatment quartiles (days)	Stage III chemoradiotherapy (N=2772)		Stage III radiotherapy (N=1359)		Stage III systemic therapy (N=907)		Stage IV systemic therapy (N=5268)	
	aHR* (95% CI)	P value	aHR† (95% CI)	P value	aHR‡ (95% CI)	P value	aHR§ (95% CI)	P value
1 (0–21 days)	Ref	-	Ref	-	Ref	-	Ref	-
2 (22–35 days)	1.06 (0.92 to 1.23)	0.4072	0.65 (0.51 to 0.82)	0.0002	0.92 (0.73 to 1.15)	0.4495	0.89 (0.82 to 0.98)	0.0169
3 (36–49 days)	1.09 (0.93 to 1.28)	0.2833	0.55 (0.44 to 0.69)	<0.0001	0.84 (0.66 to 1.07)	0.1540	0.84 (0.77 to 0.93)	0.0005
4 (>49 days)	1.12 (0.95 to 1.32)	0.1612	0.59 (0.47 to 0.73)	<0.0001	0.72 (0.56 to 0.91)	0.0062	0.77 (0.70 to 0.85)	<0.0001

*Time-to-treatment adjusted for gender, age, socioeconomic status, performance status, histology.
†Time-to-treatment adjusted for age, socioeconomic status, year of diagnosis, performance status, histology.
‡Time-to-treatment adjusted for age, performance status, histology.
§Time-to-treatment adjusted for gender, age, performance status, histology, distant metastasis (cM1a vs cM1b/cM1c), type of systemic therapy (targeted vs chemo/immunotherapy).
aHR, adjusted HR; NSCLC, non-small cell lung cancer.

Table 3 Multivariable Cox regression clinical stage IV NSCLC (subtypes of systemic therapy); (aHR (95% CI)) for mortality associated with time-to-treatment

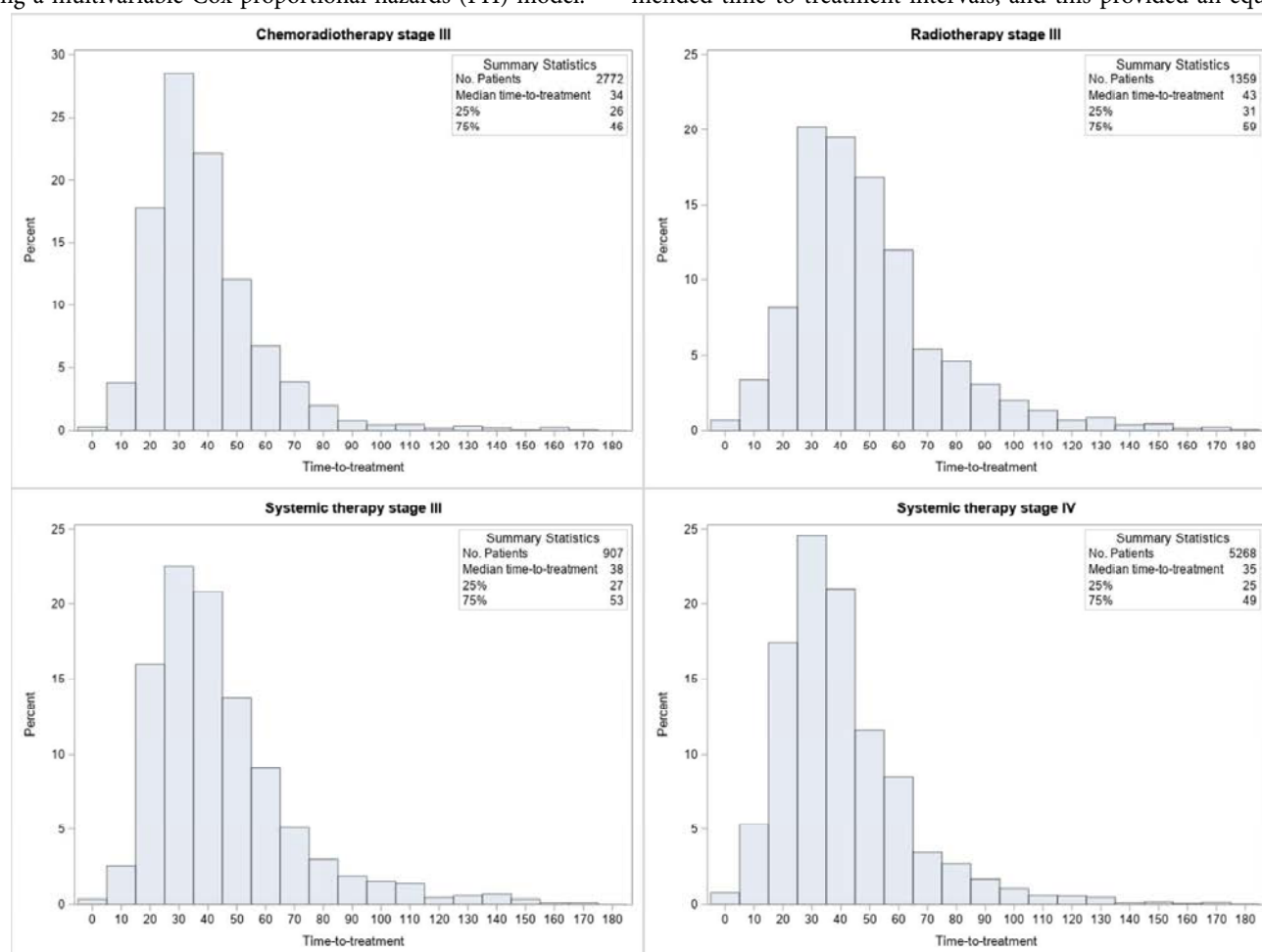
Time-to-treatment quartiles (days)	Stage IV chemotherapy and/or immunotherapy (N=3715)		Stage IV targeted therapy (N=1553)	
	aHR* (95% CI)	P value	aHR† (95% CI)	P value
1 (0–21 days)	Ref	-	Ref	-
2 (22–35 days)	0.87 (0.79 to 0.97)	0.0081	0.97 (0.81 to 1.16)	0.711
3 (36–49 days)	0.80 (0.72 to 0.89)	<0.0001	0.95 (0.78 to 1.15)	0.59
4 (>49 days)	0.72 (0.64 to 0.81)	<0.0001	0.96 (0.79 to 1.17)	0.7004

*Time-to-treatment adjusted for gender, age, socioeconomic status, performance status, histology, distant metastasis (cM1a vs cM1b/cM1c).
†Time-to-treatment adjusted for gender, age, performance status, histology, distant metastasis (cM1a vs cM1b/cM1c).
aHR, adjusted HR; NSCLC, non-small cell lung cancer.

with longer time-to-treatment. OS was calculated as the time in days between start of treatment until day of death or 1 February 2020.

First, we studied the association between time-to-treatment and OS using a multivariable Cox proportional hazards (PH) model.

Time-to-treatment was tested for data-driven quartiles (first: 0–21 days, second: 22–35 days, third: 36–49 days, fourth: >49 days) as there is a lot of (inter)national variation between recommended time-to-treatment intervals, and this provided an equal

**Figure 2** Distribution of time-to-treatment per stage and type of therapy.

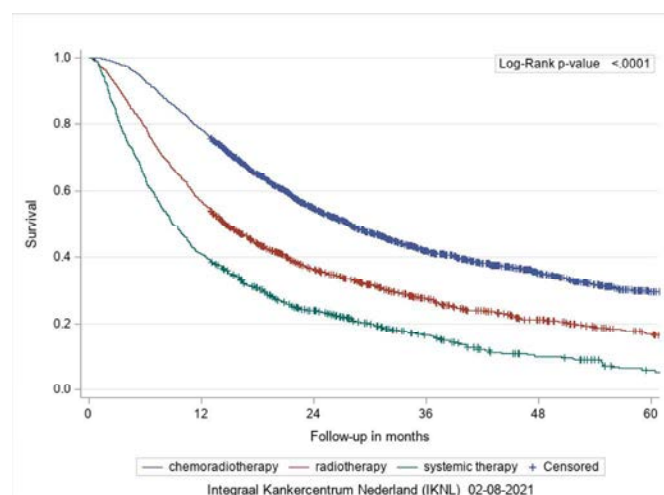


Figure 3 Kaplan-Meier plot stage III therapeutic strategies (chemoradiotherapy, radiotherapy, systemic therapy).

distribution of patients across the different intervals. This way ensured sufficient power in all categories. The first quartile served as reference. Prior to analysis, the PH assumption was examined to determine whether the HR for any parameter was constant over time. Non-proportionality was detected by a graphical approach and proportionality tests. Other covariates were selected for their prognostic association with survival by use of backward and forward stepwise selection and parameters with $p > 0.05$ were removed from the model. The covariates included in each model are cited in tables 2 and 3 may differ between the models. The dataset was stratified according to type of therapy to account for effect modification. In addition, the model of stage IV disease was extended for subtype of systemic therapy due to prognostic differences. We combined immunotherapy and chemotherapy as immunotherapy was only offered as second line therapy during the first years of the study period. The study was underpowered to perform additional analyses for stage III receiving systemic therapy. The association was determined by adjusted HRs (aHRs), 95% CI and p values. AHRs > 1.0 with $p < 0.05$ represented an increased hazard of death. We used the Kaplan-Meier method and log-rank tests to determine how OS varied with stage and type of therapy across the quartiles.

Next, we identified factors associated with a delay in time-to-treatment by multivariable analysis using multilevel logistic regression. The first quartile served as reference (ie, 0–21 days). As the data had a hierarchical structure, meaning that patients are nested within hospitals, a multilevel model was used including the hospital of diagnosis as random-effect parameter.²⁷ The analysis

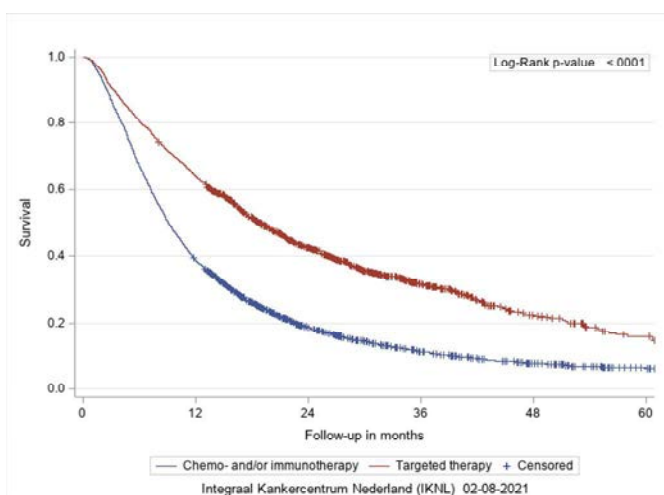


Figure 4 Kaplan-Meier plot stage IV systemic therapy (chemotherapy and/or immunotherapy, targeted therapy).

included age, gender, year of diagnosis, diagnostic staging procedures and type of therapy as fixed effects, while hospital of diagnosis was included as a random effect. The statistical significance of the fixed parameters was evaluated in forward and backward analysis. Parameters with a $p > 0.05$ were eliminated from the model. Model fit was assessed by Bayesian Information Criterion. The intraclass correlation coefficient (ICC) was calculated to quantify the fraction of the total variability in the outcome attributable to the clustering effect.²⁷

RESULTS

Patient population

This retrospective cohort (figure 1) included 10 306 patients, 57% of which were male (table 1). Median age was 68 years in stage III and 67 years in stage IV patients, and 74% of the total population was > 60 years. Forty-nine per cent was diagnosed with stage III and 51% with stage IV. For stage IV disease, distant metastases were most commonly staged as M1b (38%). This category involves patients with stage M1b according to the seventh and eighth TNM edition, meaning patients with multiple and solitary distant metastases. Of the included stage III patients, 55% received chemoradiotherapy, 27% radiotherapy and 18% systemic therapy. Other demographic and clinical characteristics are listed in table 1.

Time-to-treatment

For 53% of stage III patients and 48% of stage IV patients treatment was initiated beyond 35 days. The median time-to-treatment was 37 days (IQR: 27–51) for stage III and 35 days (IQR: 25–49) for stage IV. For stage III, median intervals per type of therapy were 34 days (IQR: 26–46) for chemoradiotherapy, 43 days (IQR: 31–59) for radiotherapy and 38 days (IQR: 27–53) for systemic therapy. Figure 2 presents the distribution of time-to-treatment per stage and type of therapy.

Time-to-treatment and survival

The median OS was 22 months for stage III and 10 months for stage IV. The 1-year, 3-year and 5-year OS rate was 71%, 37% and 25% for stage III and, 44%, 16% and 9% for stage IV, respectively. Stage III patients treated with chemoradiotherapy (1-year, 3-year and 5-year survival rates 76%, 41% and 29%, respectively) and stage IV patients treated with targeted therapy (61%, 31% and 14%, respectively) presented with better OS compared with other therapeutic strategies (figures 3 and 4). Figure 5 illustrates Kaplan-Meier plots of time-to-treatment by stage and type of therapy. For stage III patients receiving only radiotherapy or systemic therapy and stage IV patients treated with chemotherapy and/or immunotherapy, significant differences were found between the time-to-treatment intervals (log-rank $p < 0.0001$, $p = 0.003$ and $p < 0.0001$, respectively). The multivariable adjusted survival analysis showed no significant association between time-to-treatment and OS in stage III patients treated with chemoradiotherapy. In stage III patients receiving radiotherapy or systemic therapy, longer waiting times were significantly associated with a lower risk of death (radiotherapy aHR 22–35 days: 0.65, 95% CI 0.51 to 0.82; aHR 36–49 days: 0.55, 95% CI 0.44 to 0.69; aHR > 49 days: 0.59, 95% CI 0.47 to 0.73; systemic therapy aHR > 49 days: 0.72, 95% CI 0.56 to 0.91, table 3). In stage IV patients, time-to-treatment beyond 22 days was associated with a lower risk of death (aHR 22–35 days: 0.89, 95% CI 0.82 to 0.98; aHR 36–49 days: 0.84, 95% CI 0.77 to 0.93; aHR > 49 days: 0.77, 95% CI 0.70 to 0.85). Stratified analysis for subtypes of systemic therapy showed no significant association between time-to-treatment and survival for patients treated with targeted therapy. For patients treated with chemotherapy and/or immunotherapy, time intervals beyond 22 days were associated with a lower risk of death (aHR 22–35 days: 0.87, 95% CI 0.79 to 0.97; aHR 36–49 days: 0.80, 95% CI 0.72 to 0.89; aHR > 49 days: 0.72, 95% CI 0.64 to 0.81). Tables 2 and 3 show the aHRs of time-to-treatment stratified per type of therapy. Online supplemental files 1 and 2 provide insight in the dominance of covariates that were selected for multivariable analysis.

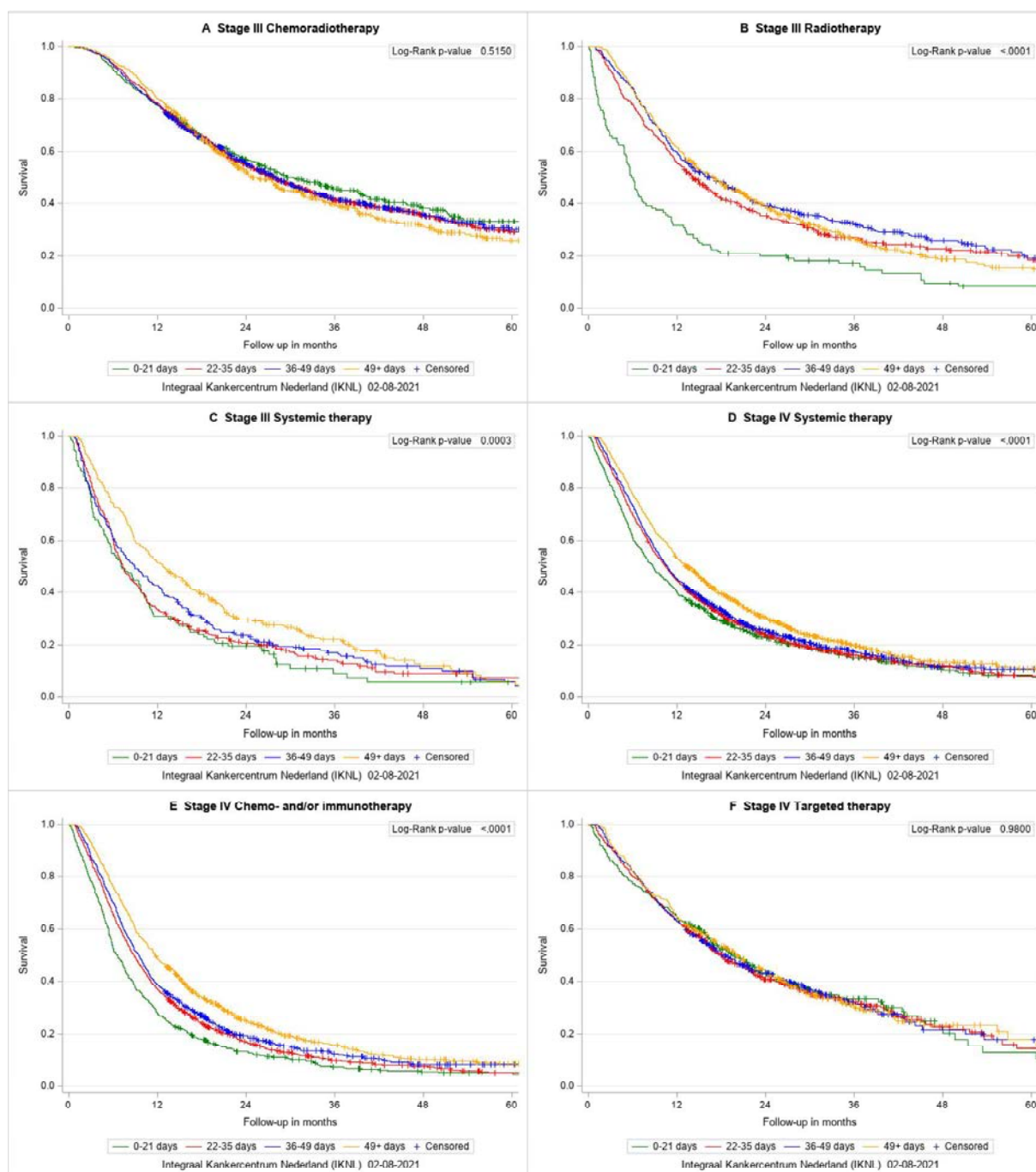


Figure 5 Kaplan-Meier plots time-to-treatment by stage and type of therapy.

Factors associated with a delay in time-to-treatment

Patient characteristics, such as age >80 years (stage III: OR 1.57, 95% CI: 1.23 to 2.02; stage IV: OR 1.79, 95% CI: 1.32 to 2.42), were a significant predictor with prolonged time-to-treatment (table 4). Also, diagnostic procedures like EBUS (stage III: OR 1.81, 95% CI: 1.58 to 2.07; stage IV: OR 1.69, 95% CI: 1.44 to 1.99), explorative surgery (stage III: OR 10.9, 95% CI: 4.02 to 29.7; stage IV: OR 8.16, 95% CI: 2.94 to 22.7) and transthoracic biopsy (stage III: OR 2.24, 95% CI: 1.72 to 2.90; stage IV: OR 2.08, 95% CI: 1.67 to 2.60) significantly increased the odds for delay. For stage III patients, treatment with radiotherapy (OR: 2.34, 95% CI: 1.99 to 2.74) or systemic therapy (OR: 1.58, 95% CI: 1.34 to 1.86) was less often initiated within the first and second quartile (≤ 35 days) compared with chemoradiotherapy.

We also found factors that were significantly associated with shorter time intervals in both stages. For stage III patients, a performance status >2 (OR: 0.62, 95% CI: 0.41 to 0.93) significantly decreased the odds for delay. For stage IV, a missing performance status (OR: 0.79, 95% CI: 0.68 to 0.94), distant metastasis staged as

M1b or M1c (OR: 0.80, 95% CI: 0.71 to 0.91) and targeted therapy (OR: 0.78, 95% CI: 0.68 to 0.89) were significantly associated with shorter intervals. Other factors are detailed in table 4. The ICC indicates that 4%–8% of the total variation in the probability of longer waiting times is accounted for by the hospital characteristics. This leaves 92%–96% to be accounted for measured or unmeasured factors others than the hospital, such as patient and tumour characteristics.

DISCUSSION

Present observational findings demonstrate a complex association between time-to-treatment and survival for advanced NSCLC. A longer time-to-treatment was significantly associated with a lower risk of death for stage III patients treated with radiotherapy or systemic therapy and for stage IV patients treated with chemotherapy and/or immunotherapy. No significant association with survival was found for stage III patients treated with chemoradiotherapy and stage IV patients treated with targeted therapy. With this study, we distinguish ourselves from others by identifying factors

Table 4 Multivariable analysis by multilevel logistic regression; factors associated with a delay in time-to-treatment

Factor	OR	95% CI	P value
Stage III (N=5038), treatment delay (>35 days)			
Age at diagnosis (years)			
61–70 vs 18–60	1.17	0.99 to 1.36	0.0548
71–80 vs 18–60	1.52	1.29 to 1.80	<0.0001
80+ vs 18–60	1.57	1.23 to 2.02	0.0004
History of other cancer			
Yes vs no	1.53	1.23 to 1.91	0.0003
Performance status			
1 vs 0	1.14	0.97 to 1.35	0.1124
2 vs 0	1.11	0.86 to 1.43	0.4305
3+4 vs 0	0.62	0.41 to 0.93	0.0223
Missing vs 0	1.01	0.85 to 1.20	0.8864
EUS			
Yes vs no	1.39	1.16 to 1.66	0.0005
EBUS			
Yes vs no	1.81	1.58 to 2.07	<0.0001
Explorative surgery			
Yes vs no	10.92	4.02 to 29.7	<0.0001
Transthoracic biopsy			
Yes vs no	2.24	1.72 to 2.90	<0.0001
Unknown vs no	0.91	0.79 to 1.05	0.2002
Type of therapy			
Radiotherapy vs chemoradiotherapy	2.34	1.99 to 2.74	<0.0001
Systemic therapy vs chemoradiotherapy	1.58	1.34 to 1.86	<0.0001
Stage IV (N=5268), treatment delay (>35 days)			
Age at diagnosis (years)			
61–70 vs 18–60	1.16	1.01 to 1.34	0.0363
71–80 vs 18–60	1.44	1.23 to 1.67	<0.0001
80+ vs 18–60	1.79	1.32 to 2.42	0.0002
Performance status			
1 vs 0	1.07	0.92 to 1.25	0.3745
2 vs 0	0.84	0.66 to 1.07	0.1539
3+4 vs 0	0.87	0.53 to 1.43	0.5741
Missing vs 0	0.79	0.68 to 0.94	0.006
Distant metastasis			
M1b/M1c vs M1a	0.80	0.71 to 0.91	0.0005
EUS			
Yes vs no	1.49	1.22 to 1.82	0.0002
EBUS			
Yes versus no	1.69	1.44 to 1.99	<0.0001
Explorative surgery			
Yes versus no	8.16	2.94 to 22.7	0.0003
Transthoracic biopsy			
Yes versus no	2.08	1.67 to 2.60	<0.0001
Unknown versus no	0.89	0.77 to 1.01	0.0778
Type of systemic therapy			
Targeted therapy versus chemo/immunotherapy	0.78	0.68 to 0.89	0.0003

The hospitals accounted for approximately 8% of the variability in time-to-treatment for stage III (ICC: $\tau_{00}=0.2815$; $z(5022)=4.70$, $p<0.0001$) (Median OR _{lowest-highest}: 0.6–1.8) and 4% for stage IV (ICC: $\tau_{00}=0.1462$; $z(5253)=4.04$, $p<0.0001$) (Median OR _{lowest-highest}: 0.6–1.7).²⁷

ORs that reached the level of significance are marked as bold.

EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound; ICC, intraclass correlation coefficient.

associated with longer time-to-treatment intervals using a multilevel approach and performing stratified analysis for stage and type of therapy.

Although we have corrected for multiple confounders, the cause of the paradoxical association remains unsolved. We believe that this complex association is probably confounded by unmeasured patient and tumour-specific factors rather than hospital related factors. Especially, as the multilevel logistic regression analyses showed a low interhospital variability, which may relate to the

well-organised healthcare and compulsory basic level of health-care insurance in the Netherlands. Clinical urgency seems to dictate timelines of treatment as advanced stage patients presenting with severe signs and symptoms receive treatment more promptly compared with fitter patients. Also, effectiveness of therapy, inherent to OS prognosis, appears to surround the paradoxical effect. Although our study finds no evidence that urgent treatment is associated with improved outcomes in advanced NSCLC, we still would like to stress the general importance of early diagnosis and treatment. Especially as cancer stage remains the most important predictor of lung cancer survival²⁸ and delays to diagnosis and treatment can cause significant emotional distress to patients and their care-givers.²⁹ Diagnostic procedures appeared to be responsible for longer waiting times. However, these factors might have resulted in the selection of more complicated diagnostic procedures for patients fit for treatment.

A recent systematic review reported that timely care was associated with worse prognosis in advanced NSCLC.²¹ This finding is in line with our results. We believe that this paradox partly relates to a sicker quicker phenomenon; More aggressive tumours are likely to cause symptoms that would draw attention to the underlying cancer and may prompt to fast diagnosis and treatment,³⁰ but would also spread more rapidly and result in poorer prognosis.^{31,32} For example, a performance status >2 in stage III patients significantly decreased the risk for treatment delay (OR 2.24, 95% CI: 1.72 to 2.90). Presence of superior vena cava obstruction may be an important indicator for prompt palliative radiotherapy in stage III NSCLC patients.³³ For stage III chemotherapy, no paradox was found as this therapy is applied to fitter patients and therefore minimises the sicker-quicker effect. Unfortunately, we could not get this information from the dataset, and we were not able to explain the exact cause since the paradox remained after correcting for factors as performance status and age. Potential unmeasured confounders surrounding the 'sicker-quicker effect' could be symptom level at presentation, therapy intent (potentially curative vs purely palliative), comorbidities, tumour biology and tumour mass.^{34–35} However, it is extremely difficult to identify and account for these (unmeasured) confounders as retrospective analysis rather catches trends than quantifies the impact at an individual level. We believe that registration studies should collect more details on patient and tumour characteristics with regard to disease progression, prognosis and comorbidities. Added, future research should focus on subgroup analysis, with respect to stage, type of therapy, therapy intent, histology, comorbidities and presence of a targetable mutation, to limit heterogeneity and quantify the impact at a more individualised level.

Discovery of new molecular alterations and development of targeted therapy demonstrated major improvements over conventional chemotherapy when applied to the appropriately selected advanced patients.^{36,37} Presence of an actionable mutation seems to affect the association between time-to-treatment and survival since we found different outcomes across subtypes of systemic therapy. This likely relates to effectiveness of therapy as the OS prognosis remains poor for patients receiving conventional chemotherapy, making time-to-treatment less relevant.^{38,39} Another potential confounder is behaviour of tumours with a targetable mutation as a longer volume doubling time was found in NSCLC patients with a positive epidermal growth factor receptor (EGFR) mutation compared with a negative mutational status (median: 676 days vs 139 days).⁴⁰ We suspect tumours with a positive mutational status to have a slowly progressive and less aggressive character. For these patients, clinicians seem to have time for optimal pretreatment assessments. While the field of targeted and immunotherapy continues to evolve and improve, time-to-treatment and its impact may also become more relevant. An ongoing evaluation of time-to-treatment and its impact on outcomes will be needed parallel to these developments.

Molecular diagnostics have become standard in clinical routine to identify patients who may benefit from targeted therapy or immunotherapy.⁷ However, previous Dutch studies showed that the molecular testing rate increased significantly from 73% in 2013 to 81% in 2017.^{41,42} Though, about 15% of the patients did not receive

targeted therapy despite presence of a targetable mutation.⁴³ This suggests a suboptimal diagnostic pathway in the past years that might have affected patient outcomes and potentially acts as a confounder in relation with time-to-treatment.

The strengths of our study mainly relate to the nationwide coverage of the database. We have created a platform that can be used in future research to restudy the impact of time-to-treatment on advanced NSCLC. Due to the large sample size, we were able to stratify analysis without being underpowered. Added, the availability of a broad range of patient variables in the NCR database enabled us to account for various potential confounders. Also, we selected a recent patient cohort to ensure that our data reflects the current clinical situation. Thereby, all patients included had equal access to oncology care as health insurance is obligated in the Netherlands. Next, we evaluated the complete timeframe as we used first outpatient visit for the suspicion of lung cancer as starting point of the interval. Last, we have tried to correct for immortal time bias by calculating the OS for every patient from start of treatment. However, measuring survival from the start of treatment does not account for the group of patients that deteriorated before having treatment. One way to do this is to stratify analysis by histology, stage and comorbidity as this limits confounding by not including a heterogeneous group of stages or treatments.⁴⁴ Yet, we have prioritised stratification for stage and type of therapy as we lack power for histology. Alternatively, we adjusted for histology in our multivariable analysis. Future research should focus on subgroup analysis and the relationship between diagnostic delays and deterioration of performance status over time.

This study also has some limitations. For instance, detailed information on comorbidities, smoking information, lung function test and psychosocial status are not available in the NCR, therefore limiting the possibility to explore the impact of these variables. Especially psychosocial status is of particular importance in pretreatment assessment when considering patients' perspective.²⁹ Delay in time between diagnostic workup and start of treatment is undesirable as this potentially causes significant emotional distress and impaired health-related quality of life. Also, information on performance status and transthoracic biopsy is missing for a subgroup of patients as the NCR started this registration since 2015 and 2017, respectively. As these subgroups consisted of relatively high numbers of patients, we classified the status as unknown rather than exclude them from analysis. Excluding patients with missing data from the analysis provided similar results. Last, our findings were obtained in a country with universal public healthcare and can therefore only be generalised to countries with a similar healthcare status.

CONCLUSION

Our study finds no evidence that a more rapid start of treatment improves outcomes in advanced NSCLC. A paradoxical effect was seen for stage III patients treated with radiotherapy or systemic therapy and stage IV patients receiving chemotherapy and/or immunotherapy: survival was better in patients with longer time-to-treatment. The benefit of urgent treatment is probably confounded by unmeasured patient and tumour characteristics, and clinical urgency dictating timelines of treatment. Patients presenting with severe signs and symptoms seem to receive treatment more promptly compared with fitter patients. Despite our findings, clinical timeliness should still be approached carefully for each patient to ensure accurate and timely care. Future research should focus on subgroup analysis, with respect to stage, type of therapy, therapy intent, histology, comorbidities and presence of a targetable mutation, to quantify the impact at a more individualised level. As therapeutic strategies for advanced NSCLC continue to evolve and improve, also time-to-treatment and its impact may become more relevant. Therefore, an ongoing evaluation will be needed.

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ARTIGO ORIGINAL

Otimizar os serviços desencadeados pela falta de ar em pessoas mais velhas com doença avançada: um estudo económico multicêntrico (OPTBreathe)

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RESUMO

Objetivos Insuficiência Contexto Na doença avançada, a falta de ar torna-se grave, aumentando o recurso aos serviços de saúde. Os serviços desencadeados pela falta de ar demonstram eficácia em ensaios e meta-análise, mas carecem de avaliação económica.

Métodos O nosso estudo económico incluiu uma experiência de escolha discreta (EED), seguida por uma modelação de análise custo-eficácia. A EED incluiu entrevistas presenciais com pacientes mais velhos com falta de ar crónica e seus cuidadores em 9 centros no Reino Unido. A análise de regressão logística condicional dos dados da EED determinou as preferências (ou não, indicadas por coeficientes beta negativos) para os atributos do serviço. A modelação económica estimou os custos e os anos de vida ajustados à qualidade (QALY) ao longo de 5 anos.

Conclusões A EED recrutou 190 pacientes e 68 cuidadores. A oferta de serviços de falta de ar em pessoa de cirurgias de médicos de clínica geral não foi preferida ($\beta = -0,0$, IC 95% $-0,40$ a $-0,21$). A preferência foi para estabelecimentos hospitalares ambulatoriais (0,16, 0,06 a 0,25) ou visitas a domicílio (0,15, 0,06 a 0,24). Os serviços presenciais com revisão abrangente do tratamento (0,15, 0,07 a 0,21) e o apoio holístico (0,19, 0,07 a 0,31) foram preferidos em relação aos que não os tinham. A análise de custo-eficácia concluiu que os modelos mais e menos preferidos de serviços relacionados com a falta de ar foram mais económicos em comparação com os cuidados habituais. O serviço preferido apresentou custos £5719 mais baixos (IC 95% -6043 a 5395), com benefícios QALY de 0,004 (IC 95% $-0,003$ a $0,011$) por paciente. A adoção foi mais elevada quando os atributos foram personalizados de acordo com as preferências individuais (86% vs. 40%).

Conclusão Os serviços de falta de ar são mais económicos em comparação com os cuidados habituais de saúde e sociais, tendo em conta a poupança de custos e a melhor qualidade de vida. A adoção de serviços de falta de ar foi mais elevada quando os atributos do serviço foram personalizados.

INTRODUCTION

Breathlessness is common in respiratory diseases and many other conditions.¹ In the advanced stages of illness, breathlessness often becomes severe, debilitating and frightening, resulting in emergency visits and hospitalisations.^{2–5} When breathlessness continues despite optimal treatment of the underlying condition, it is often referred to as chronic or refractory.^{6,7} People with such breathlessness often have multiple symptoms, which increase as their disease progresses. Breathlessness results in high costs to health and social care systems. It affects family members and those close to the patients (hereafter called carers), with high informal care costs that increase overall societal costs by >250%.⁸

Consequently, a holistic approach involving early palliative care is often proposed as beneficial in ad-

Key messages

What is already known on this topic

- Holistic short-term multiprofessional breathlessness triggered services reduce distress and the psychological outcomes of anxiety and depression in patients with chronic breathlessness.

What this study adds

- We propose the most cost-effective models of breathlessness services by identifying attributes to prioritise, especially with limited resources, and by conducting Markov modelling.

How this study might affect research, practice or policy

- Breathlessness services favoured by patients and carers are in accord with clinician recommendations for comprehensive treatment review, a holistic approach to manage breathlessness and a flexible individual approach.
- Breathlessness services offer cost savings in healthcare of more than £50 000 for every quality-adjusted life year gained.

vanced respiratory disease.⁹ A meta-analysis including 37 articles trialling 18 services found that holistic short-term multiprofessional breathlessness triggered services (BSs) reduce distress in patients with chronic breathlessness due to advanced diseases and the psychological outcomes of anxiety and depression.¹⁰ These services, such as the London-based BS and those in Australia, New Zealand and Germany, combine expert respiratory, palliative and therapy (physiotherapy and occupational therapy) assessment and review, plus a toolkit of evidence-based, non-pharmacological and pharmacological interventions.^{7 11–16} However, a Delphi exercise found divergent expert opinions about how services might be best provided, especially whether these should be from general practitioner (GP) surgeries, outpatient clinics or directly to people's homes.⁹ There is no evidence of which service attributes to prioritise, especially with limited resources. Cost-effectiveness data to inform decision-making are lacking. Therefore, the study to optimise cost-effective support for older patients with refractory breathlessness (OPT-Breathe) aimed to identify what attributes of BSs patients and their carers value most. We then aimed to conduct an economic evaluation of BSs in order

to propose the most cost-effective models of BSs based on clinical effectiveness and available resources.

METHODS

This economic study had two components: a discrete choice experiment (DCE)^{17–19} to determine the attributes influencing preferences for BSs, followed by a cost-effectiveness Markov modelling. DCE is a quantitative method increasingly used by health economists and in healthcare to elicit participants’ (patients, payers, carers) relative preference weights for service attributes that will affect their use, without directly asking them to state their preferred options. In a DCE, participants are presented with alternative hypothetical scenarios containing different attributes.

Participants make a choice between competing scenarios, each of which consists of a combination of the studied attributes. Using the derived parameters from the DCE results, combined with epidemiological data and existing trial data, Markov modelling²⁰ (online supplemental figure S2) was conducted to determine cost-effectiveness.^{6,21,22} Markov modelling is an analytical framework frequently used in economic evaluation of healthcare interventions. Reporting follows the Consolidated Health Economic Evaluation Reporting Standards,²³ Conjoint analysis checklist²⁴ and the guidelines for decision analytic modelling²⁵ (see the Ethics approval section).

DCE to elicit preference and acceptability

The DCE sought to determine (1) the absolute and relative importance of attributes, (2) the willingness to wait for attributes, and (3) the probabilities of uptake (ie, level of acceptance) of varying packages of BSs.

Definition of attributes

Attributes were built on findings from literature reviews, service modelling, consultation with this study’s collaborators and patient experts, and data from the trial of BS,¹¹ including qualitative interviews with patients.^{12,13,15} Preliminary secondary analysis of these data and review by our patient and public involvement and engagement (PPIE) group suggested that the key attributes should be grouped according to place of consultation, nature of treatment

review, additional support offered, expectation for change in breathlessness and expectation for change in healthcare use (see figure 1). The PPIE input revised the descriptive words used. We prepared hypothetical choices, with six sets per participant, for the DCE (see online supplemental figure S1 for details).

DCE settings

The study was opened in nine participating study sites across the UK, with a mix of urban and more rural areas (online supplemental table S1), including respiratory medicine and lung cancer clinics, palliative care services, from patients admitted to hospital for breathlessness, physiotherapy services, and integrated respiratory teams.

DCE participants

We recruited consenting patients who were 65 or older, with a medical diagnosis of COPD, lung cancer or interstitial lung disease (ILD), and with breathlessness refractory to optimal medical management in the view of the treating clinician, with a severity level of 2, 3, 4 or 5 on the Medical Research Council Dyspnoea Scale. Sample size calculation is described in online supplemental file 1.

We also recruited a consenting family member/friend/lay carer who was designated as the closest family member or caregiver to the participating patient. Patients with breathlessness of unknown cause, with chronic hyperventilation syndrome, or without capacity to fully comprehend and retain information about the study or those unable to engage in an interview were excluded.

All interviews were conducted face-to-face using a standard questionnaire specifically designed for the project, asking for experiences in managing breathlessness, questions about service use, and clinical and sociodemographic information, in addition to six choice questions of the DCE, as well as open questions for explanation (reasons for choice) and expansion (other comments). Details of administration of the DCE questionnaires and data collection are found in online supplemental file 1.

Analysis of choice question data

We described the characteristics of patients and carers and examined if anyone chose ‘neither’ in all six choices. We used a

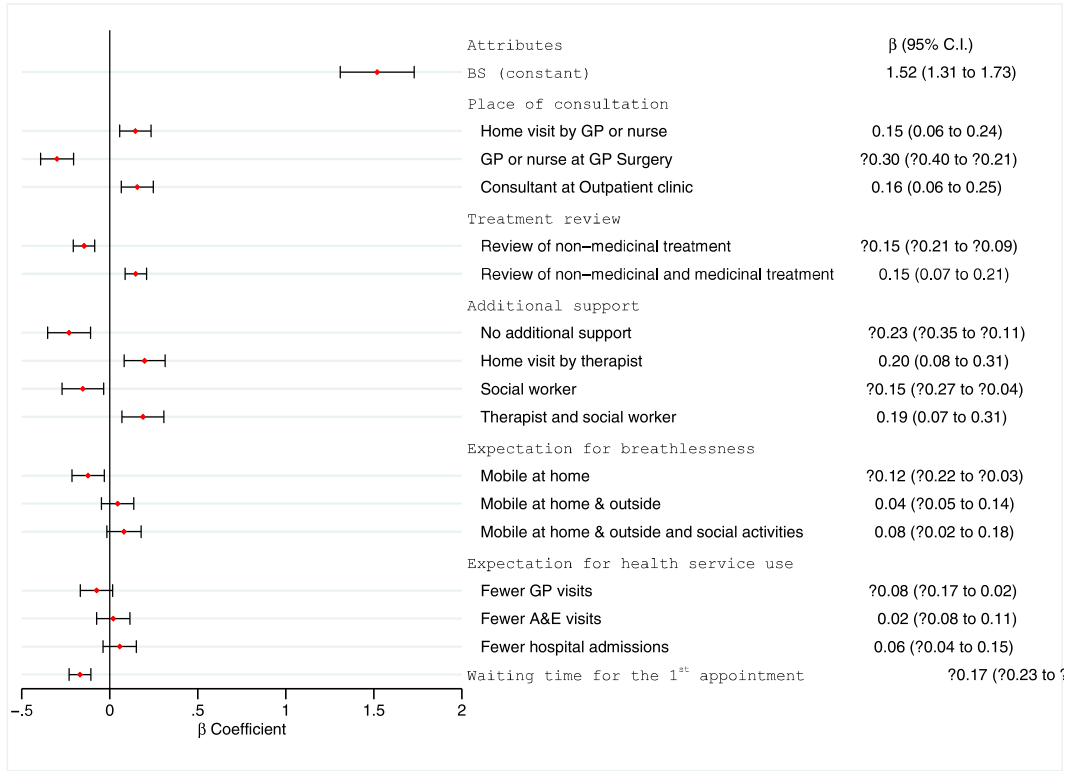


Figure 1 Preferences for attributes and levels of breathlessness service: results of the regression analysis from all patients and carers. The sign and magnitude of coefficients indicate the direction and strength of preferences for each attribute. Positive coefficients represent the degree of preference for the corresponding attribute and negative coefficients the degree of ‘negative preference’ or rejection of the corresponding attribute. A&E, accident and emergency; BS, breathlessness service; GP, general practitioner.

conditional logit model with individual fixed effects, considering the independence of irrelevant alternative, random taste variation (each respondent has different coefficients) and multiple observations from the same respondent. The magnitude and sign (+/−) of the coefficients on the attributes and the levels represent the strength and direction of preferences. The strength of preference can be inferred from the magnitude of the coefficients and the order of preference for attributes or levels can be established. After obtaining coefficients on the attributes and their groups, representing the relative weights in utility from the BS, we calculated the probability of acceptance of the proposed BS, to be used in the Markov model. We also calculated the CI for probabilities using bootstrapping.

Subgroup analyses were conducted by patients and carers, London-based and non-London-based, and gender of the patients. All analyses were conducted using STATA V.16.

Analysis of text from open-ended questions

To explore the reasons why patients and carers chose certain options, free-text answers to the questions, asking respondents to make comments or suggestions regarding services to manage breathlessness, were analysed using a thematic analysis approach.

Economic modelling for cost-effectiveness

We developed a Markov model to simulate the effect of BS in a cohort of patients and to estimate the cost-effectiveness of different models of BS compared with usual care. We populated the model with data from the breathlessness trial (of a holistic multiprofessional service where patients with severe continuing breathlessness were referred)⁶ and published mortality rates (see online supplemental tables S2 and S3). The analysis was conducted from a national health service perspective.

Development of model structure

We defined a starting cohort by sample characteristics (eg, 75-year-old men with COPD), reflecting the epidemiology of a disease. The transition states in the Markov model were defined mutually exclusive (eg, receiving usual care, death). Intervention (taking up BS plus usual care) and associated states (eg, stable with improvement, stable with extended effects, no change) were also defined. Cycle length was set as 12 weeks (or 3 months) and we used 20 cycles (or 5 years) for time horizon to capture the clinical problems and intervention effects. We assumed that the effects of BS disappear after 12 weeks (first cycle) in case of the BS plus and usual care. For BS with a lasting effect scenario, we assumed that the effects of BS lasted another 12 weeks and disappear after the second cycle. We used age-specific and sex-specific all-cause mortality in the initial stage and used age-specific and sex-specific respiratory mortality (online supplemental table S3) in later stages. The yearly discount rate of 3.5% was applied considering a cycle length of 0.25 years.

Incremental costs per quality-adjusted life years

We used the EuroQol-5 Dimension (EQ-5D) index scores and health and social care costs in the BS plus usual care group and the usual care only group before and after a BS in the trial data. Using Monte Carlo simulation with 1000 in the defined cohort, we estimated the incremental cost-effectiveness ratio (ICER), which is defined as: (cost of intervention–cost of control) divided by (effect of intervention–effect of control).

Integration of results from the DCE

The probability of acceptance was calculated for the most acceptable BS, and the least acceptable BS, and used in the Markov model to examine changes in the cost-effectiveness of the BS with given configurations.

Sensitivity analysis

To assess the robustness of the results to the realistic variations in the level of underlying data, we conducted a sensitivity analysis. We estimated the model for a different cohort (75-year-old women

with COPD) and for two different configurations of BS as deterministic sensitivity analysis. CIs around costs and quality-adjusted life years (QALYs) were calculated using delta methods (see online supplemental table S5). For uncertainty around the ICER, the cost-effectiveness acceptability curve (CEAC) against willingness to pay was explored. We used Treeage Pro Software V.2020 for this modelling.

RESULTS

Discrete choice experiment

We recruited 190 patients and 68 carers: 130 patients had COPD, 18 had ILD and 40 had lung cancer (with 2 missing) (table 1). Patients had a mean age of 75 years, 35% were women and 30% were living alone. Of the patients, 21% were widowed and 62% were married/partnered, and 85% were living comfortably or coping on present income. Carers were on average 64 years old and 86% were women. Two-thirds of the carers were spouse/partner and 21% were daughter/son, and 90% had a religious faith. In this study, 49% of the patients and 66% of the carers were recruited from hospitals in the London area.

In the final analysis, 1535 choice questions or 4605 observations from 256 participants were used. The frequencies of each attribute (online supplemental table S4) did not show the main drivers of choices.

Importance of attributes of BS

Respondents had a strong preference for any combinations of BS ($\beta=1.52$, 95% CI 1.31 to 1.73; figure 1), indicating that respondents always wanted BS. BS offered at GP surgeries was not preferred (showing a negative preference; $\beta=-0.30$, 95% CI -0.40 to -0.21). In contrast offering BS was preferred at hospital outpatient clinics ($\beta=0.16$, 95% CI 0.06 to 0.25) or via home visits ($\beta=0.15$, 95% CI 0.06 to 0.24). BS with comprehensive treatment review ($\beta=0.15$, 95% CI 0.07 to 0.21) and holistic support ($\beta=0.19$, 95% CI 0.07 to 0.31) was preferred to usual services. Respondents did not prefer BS with no additional support ($\beta=-0.23$, 95% CI -0.35 to -0.11) or with social workers alone ($\beta=-0.15$, 95% CI -0.27 to -0.04).

Probability of taking up various BS

The least valued BS was determined, according to the estimated coefficients, as the services offered at GP surgeries, reviewing non-medical treatment, no additional support and 8 weeks of waiting time for the first appointment. The probability of taking up such BS was 40.4% (1 in figure 2). As patients and carers valued review of medicinal (pharmacotherapy) treatment, support from therapists and social workers, and shorter waiting time, the probability of taking up BS increased from 1 to 5 incrementally (figure 2). For example, when reviewing medicinal treatment was added to the BS, the probability of uptake increased to 47.7%. The most preferred configuration of the BS was where patients visit outpatient clinics to see consultants, review of both medicinal and non-medical treatment, support by a physiotherapist, an occupational therapist and a social worker, and with 2 weeks to wait to get the first appointment (figure 2). It needs to be noted that BS configuration 6, offering home visits instead of appointments at outpatient clinics, had a probability of uptake as high as BS configuration 7 (figure 2). Patients and carers preferred to see consultants at outpatient clinics, but were willing to choose to take part in BS when home visits were provided.

Subgroup analysis

Carers had preferences different from patients (log likelihood ratio test: $X^2=21.77$, $p<0.04$; see online supplemental table S6). Carers stated a stronger preference for BS with home visits from GPs, both medicinal and non-medical review, and involvement from social workers and therapists, than were patients. Overall preferences of female patients differed from those of male patients (log likelihood ratio test: $X^2=797.69$, $p<0.001$; see online supplemental table S7). Women preferred home visits and social workers along with therapists, while men preferred outpatient clinics and therapists only. There was no overall difference in recruitment site (London and

Table 1 Characteristics of patients and carers who participated in the survey

	Patients (n=190)	Carers (n=68)
Diagnosis*		
COPD	130 (69)	32 (47)
Interstitial lung disease	18 (10)	14 (30)
Lung cancer	40 (21)	22 (33)
Age†	74.9 (6.1)	64.0 (13.5)
Male/female†	124 (65)/66 (35)	9 (14)/55 (86)
Ethnicity		
White	180 (95)	61 (90)
Non-white	8 (4)	7 (10)
Marital status		
Single	15 (8)	8 (12)
Widowed	39 (21)	
Married/partnership	118 (62)	59 (87)
Divorced/separate	18 (9)	1 (1)
Financial status‡		
Living comfortably on present income	77 (41)	30 (45)
Coping on present income	86 (45)	23 (34)
Difficult on present income	10 (5)	8 (12)
Very difficult on present income	2 (1)	2 (3)
Do not know	2 (1)	
Refusal/prefer not to say	6 (7)	4 (6)
Educational attainment*		
Left school at 15 years old or under	119 (63)	26 (38)
Left school at 16–17 years old	45 (24)	19 (28)
Left school at 18–19 years old	5 (3)	4 (6)
Postsecondary/vocational qualifications	8 (4)	8 (12)
University	12 (6)	11 (16)
Religious faith (=1 if yes)†	97 (51)	35 (52)
Living alone (=1 if yes)	57 (30)	0 (0)
Study site		
London	93 (49)	45 (66)
Other areas of England	97 (51)	23 (34)
Relationship to patient†		
Spouse/partner		46 (68)
Son/daughter		14 (21)
Parent		2 (3)
Friend		1 (1)
Others		2 (3)

Mean (SD) for age; n (%) for the rest.

*Two missing in diagnosis and one in educational attainment in the patient group.

†Two missing in age, four in female, one in financial status, one in religious faith and three in relationship to the patient in the carer group.

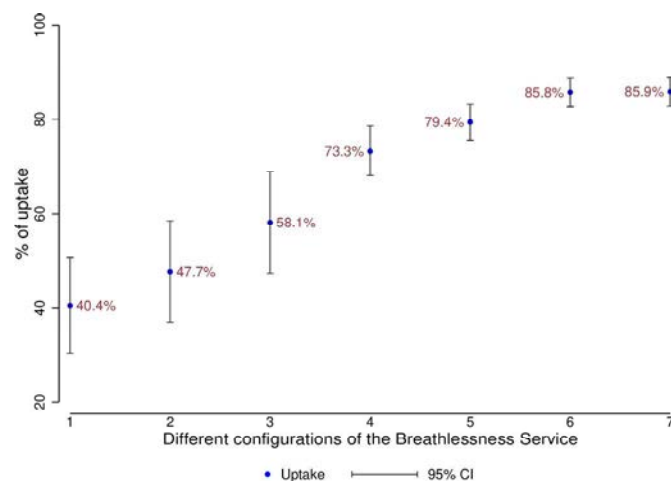


Figure 2 Probabilities of taking up breathlessness triggered services (BSs) with different configurations of attributes. Two attributes were fixed: expectation for breathlessness as 'being more mobile at home & outside and enjoying social activities' and expectation for health service as 'having fewer hospital admissions'. Example of BS: (1) general practitioner (GP) surgery, review of non-medicinal treatment only, no additional support and waiting for 8 weeks to have the first appointment; (2) GP surgery, review of non-medicinal treatment and medicinal treatment, no additional support, and waiting for 8 weeks to have the first appointment; (3) GP surgery, review of non-medicinal treatment and medicinal treatment, support from therapists and social workers, and waiting for 8 weeks to have the first appointment; (4) GP surgery, review of non-medicinal treatment and medicinal treatment, support from therapists and social workers, and waiting for 4 weeks to have the first appointment; (5) GP surgery, review of non-medicinal treatment and medicinal treatment, support from therapists and social workers, and waiting for 2 weeks to have the first appointment; (6) home visit by a GP or a nurse, review of non-medicinal treatment and medicinal treatment, support from therapists and social workers, and waiting for 2 weeks to have the first appointment; and (7) visit to outpatient clinic, review of non-medicinal treatment and medicinal treatment, support from therapists and social workers, and waiting for 2 weeks to have the first appointment.

of infection. Eleven patients wanted to have all the treatments and services at home.

Markov model estimation

Cost-effectiveness from deterministic analysis

We built a Markov model based on three alternatives: status quo (usual care), BS and BS with extended effects (the 3rd branch in the online supplemental figure S3). When the Markov model was estimated for a 75-year-old man over 5 years, the difference in costs between usual care only (no BS) and BS plus usual care was -£663 (95% CI -1076 to -250), and that between usual care only and BS with extended effects plus usual care it was -£5086 (95% CI -5469 to -4703) (table 2). The difference in QALYs was 0.013 (95% CI 0.004 to 0.022) in both cases. For women, the difference in costs was -£749 (95% CI -1100 to -398) and -£5719 (95% CI -6043 to 5395), and the difference in QALYs was 0.013 (95% CI 0.005 to 0.021) and 0.004 (95% CI -0.003 to 0.011), respectively (table 2). As changes in costs were negative and changes in QALYs were positive, providing BS to 75-year-old adults for 12 weeks was cheaper than usual care and the quality of life improved when considering the uptake chances of this population. Negative ICERs with lower costs and better outcomes in BS imply that offering BS to 75-year-old adults is cost-effective (see online supplemental table S5 for details).

When the CEACs were explored for each scenario to examine the uncertainty around the ICER, the acceptability was 1 (complete acceptance) in the ranges of willingness to pay.

other areas of England) (log likelihood ratio test: $X^2=8.58$, $p<0.73$; see online supplemental table S8).

We defined the base cases in modelling using these findings (difference between female and male patients and no difference between London and other areas of England). In other words, the take-up of BS in the 'male 75' group was derived with estimated results from male patients at all sites.

Analysis of free-text comments

Sixty-four participants provided free-text comments and 158 made suggestions for future BSs. Regarding the reasons for preferring hospital outpatient clinics or home visits to GP surgeries, respondents felt that GPs could not provide specialist care for breathlessness and said they try to avoid visiting GP due to a perceived risk

DISCUSSION

This multicentre study is the first to provide a comprehensive economic assessment of BSs for advanced diseases. It couples patient and carer preferences with cost-effectiveness modelling to determine optimal configurations for BSs. Patients and carers valued any configurations of BS over usual care. They preferred BS offering consultations at outpatient clinics or by home visits rather than at GP surgeries and wanted review of both medicinal (pharmacotherapy) and non-medicinal treatments and holistic support from therapists and social workers. The Markov model estimated the cost-effectiveness beyond the trial period (12 weeks) for up to 5 years and found that BS was cost-effective and could contribute to savings in health and social care systems.

COPD accounts for £800 million in direct healthcare costs in the UK.²⁶ The indirect costs of COPD are substantial (24 million lost working days per annum).²⁷

Costs rise in advanced diseases.²⁸ Therefore, finding cost-effective solutions is essential. There is good evidence regarding pulmonary rehabilitation in earlier stages of disease.²⁹ However, uptake of pulmonary rehabilitation varies, especially in advanced diseases where patients find it difficult to leave home. Our results indicate that in the advanced stages of disease BSs provide cost savings and better quality of life, even in instances of lower uptake at only ~40%. When the uptake is higher, savings and quality of life improvements are greater. BSs are designed to be a brief intervention, with usually around three in-depth contacts, with a longer lasting impact due to the focus on continuing patient self-management and empowerment.^{9 11 12}

We were surprised to find that patients and carers preferred BS at outpatient clinics or via home visits and not at GP surgeries. Free-text answers supported this finding: patients and carers thought that GPs were not the experts in breathlessness management and that visiting GP surgeries might risk contracting infections. This finding is at odds with a Delphi exercise with clinicians which suggested that BSs should be integrated into existing GP services.³⁰ However, our DCE findings based on patient preferences are in accord with clinician recommendations for a comprehensive treatment review, a holistic approach to manage breathlessness and a flexible individual approach. The risk raised by patients of infection in GP surgeries and possibly hospitals is brought clearly into focus by the COVID-19 pandemic. BSs offered online or remotely, or from treatment hubs, might be a good alternative. These could reduce the need for travel and allow a combined expert and GP review. Efficient community services providing virtual at-home services with shorter waiting time could encourage patients to take up BS and be a future model. Our results also highlight the importance of responding to patient preferences, with estimated uptake doubling (from 40% to 86%) when the most preferred type of service was offered.

We assessed the cost-effectiveness of BSs beyond the time horizon used in the trials, conducting cost-effectiveness analysis with a Markov model. This helps commissioners and healthcare professionals decide to adopt BSs in their communities. We used the actual views from patients and carers in the decision process in the cost-effectiveness analysis by incorporating the uptake rates of the BSs calculated from the DCE data. Unlike the assumptions or scenarios usually used in this type of analysis, we calculated the cost-effectiveness of BSs based on the stated preferences of patients and carers, which can be realistic. Our study has several limitations. DCEs suffer from hypothetical bias; our respondents may not have selected what they would do in reality. We assuaged this bias by including only older individuals with relevant illnesses and moderate to severe breathlessness, who therefore had experience of the relevant services and health problems and so were better able to judge the situation.

We also explored the reasons for choices in open comments. This enriched the data and suggests ways in which some negative preferences, such as for GP surgeries, may be overcome, for example by reducing the risk of infection in waiting rooms and providing expert support at GP surgeries. We included both pa-

Table 2 Cost-effectiveness of the breathlessness service (BS) for 5 years: results of the Markov model estimation

	Usual care only vs usual care plus BS	Usual care only vs usual care plus BS with lasting effects
75-year-old man, p(uptake)=0.85		
Costs (£)	−663 (−1076 to −250)	−5086 (−5469 to −4703)
Health outcomes (QALY)	0.013 (0.004 to 0.022)	0.013 (0.004 to 0.022)
ICER (£/QALY)	−50 789	−389 776
75-year-old woman, p(uptake)=0.87		
Costs (£)	−749 (−1100 to −398)	−5719 (−6043 to 5395)
Health outcomes (QALY)	0.013 (0.005 to 0.021)	0.004 (−0.003 to 0.011)
ICER (£/QALY)	−56 242	−1 454 683
95% CIs are in parentheses. BS is designed to involve consultations with a specialist at an outpatient clinic, review of both medicinal and non-medicinal treatments, home visits by therapists, and support from a social worker. Costs were calculated based on the National Health Service (NHS) reference costs, and unit costs of health and social care by the Personal Social Services Research Unit (PSSRU). Better mobility and independence at home and outside home and more social activities are anticipated. Fewer hospital admissions are expected and patients need to wait 2 weeks to get the first appointment. $ICER = (costs_2 - costs_1) / (QALY_2 - QALY_1)$, where 1 and 2 represent alternatives compared. Costs are in 2014 British pound sterling. ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years.		

tients and their carers; carers may play an important role in influencing patient preferences and choices.³¹ We found some differences in preferences between patients and carers regarding BS composition. Neither preferred GP surgeries; however, compared with patients, carers had a slightly stronger preference for home visits and social worker involvement. The preference for social worker involvement may reflect carer-specific supportive needs.

We need to consider how our sample represents the population of interest. We identified patients via nine centres across England: South East, Midlands, East and North East, as well as London. When compared with the national audit data,³² our sample was slightly older (75 years vs 71 years) because we intendedly approached older adults, being of specific interest and often less able to attend pulmonary rehabilitation and similar services. In our sample, 49% of patients and 66% of carers were recruited from London. Other patients were more often recruited from hospital centres from urban UK populations. According to population statistics, only 17% of the UK live in rural areas and 68% of the world population will live in cities by 2050. Therefore, our data are highly relevant to most people affected by severe breathlessness. Our results may not be generalised to rural areas; further research would need to investigate this. We found no differences between London and other areas of England, a finding supported by the similar referral rates for pulmonary rehabilitation (20% in London and 19% in the rest of England in the UK quality indicator data).³³

Cognitive burden can be a limitation when conducting DCEs, especially among older adults with chronic or advanced diseases. We determined the number of choice questions and attributes by detailed piloting. We trained research nurses, emphasising the risks of cognitive burden and offering rests, etc. One indicator of burden is poor question completion rates. We obtained rich data, with only one choice question unanswered. Therefore, we found that DCEs can be used for older adults with advanced diseases. These produced important information regarding service development and planning, which could inform future research methods.

In the modelling, we used a 5-year time horizon, although survival of patients with advanced diseases (eg, ILD, lung cancer) could vary and in instances would be shorter. We modelled different time periods of the effect of BS, including only 12 weeks. When we assumed that the effects of BS lasted longer (than 12 weeks), the cost savings were larger. BSs warrants future research with longer

follow-up periods, which examines the effects of boosts of BSs such as a follow-up or refresher consultation, including mortality. We did not include social care costs, informal care costs or costs from lost productivity.

Caution is needed regarding the shift of costs between different care settings (eg, hospital, community, home) or from formal to informal care. However, the BS trial did not find an increase in informal care costs in the intervention arm⁶ and if anything our cost savings are likely underestimated.

Data were collected before the COVID-19 pandemic, which has changed the values and attitudes towards services and the risk of infection. However, our data can be considered in the light of these changing attitudes and can help shape breathlessness services in COVID-19 pandemic situations to better help support patients with long-lasting breathlessness and their carers.

CONCLUSION

Patients with chronic breathlessness and their carers valued and accepted BSs, which were cost-effective, offering lower costs and better quality of life (savings of £50 000 per patient, plus additional QALY) compared with usual care. The uptake and cost-effectiveness of BSs are higher when services are tailored to individual preferences, with uptake increasing from 40% to 86%.

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Collaborators OPTBreathe collaborators: Noel Baxter, Surinder Birring and Irem Patel.

Contributors IJH and DY were co-chief investigators and grant leads. IJH was the study PI for the sites in London. DY coordinated the data collection in different sites and led the analysis. IJH and DY wrote the initial version of the manuscript, with contributions from CCR and GW. CCR provided additional clinical insights into the BS, interpretation of the BS trial data and DCE choices. DY led the PPIE workshops to review DCE attributes and Markov modelling. IJH and DY had full access to all the data in the study and take responsibility for the integrity of the data and analysis. DY, IJH and CCR carefully considered the response to referees' comments, conducted further analysis and led the revision of the manuscript and supplementary files accordingly. All authors contributed to the development of study aims, integration of the interpretation and analysis plan, and provided critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. IJH accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the West of Scotland Research Ethics Service (reference number: 17/WS/0083). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed. Data availability statement Data are available upon reasonable request. We can share the protocol, consent form, analysis plan, training and other relevant DCE materials. Data from the survey are approved for use by the research team and appropriately qualified researchers trained and supervised by them. Fully anonymised data with other studies for secondary analysis could be considered. De-identified participant data will be made available to bona fide researchers registered with an appropriate institution within 3 months of publication. However, the research team will need to be satisfied that any proposed publication is of high quality, honours the commitments made to the study participants in the consent documentation and ethical approvals, and is compliant with relevant legal and regulatory requirements (eg, relating to data protection and privacy). The research team will have the right to review and comment on any draft manuscripts before publication. Data will be made available in line with the policy and procedures of the Cicely Saunders Institute of Palliative Care, Policy and Rehabilitation. Those wishing to request access should email deok_hee.yi@kcl.ac.uk.

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ARTIGO ORIGINAL

Seguimento longitudinal de síndrome de COVID-19 pós-aguda: anomalias na DL_{CO}, na qualidade de vida e na troca de gases pulmonares por RM

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RESUMO

Foram observadas anomalias no rácio dos glóbulos vermelhos para o tecido plasmático alveolar (RBC:TP) por RM ¹²⁹Xe em pessoas ainda hospitalizadas e nunca hospitalizadas com síndrome de COVID-19 pós-aguda (SCPA). Contudo, não é conhecido se essas anomalias veem os seus sintomas resolvidos e se as classificações de qualidade de vida melhoram. Avaliámos 21 participantes com SCPA 7 ± 4 meses (cenário de base) e 14 ± 4 meses (seguimento) pós-infecção. Foi observada uma capacidade de difusão do pulmão para o dióxido de carbono (DL_{CO}, Δ = 14%_{pred}; IC 95% 7 a 21, p<0,001), dispneia pós-esforço (Δ = -0,7; IC 95% = -0,2 a -1,2, p=0,019), resultados do St George's Respiratory Questionnaire (SGRQ Δ = -6; IC 95% = -1 a -11, p=0,044) significativamente melhorados, mas não RBC: TP (Δ = 0,03; IC 95% = 0,01 a 0,05, p=0,051) aos 14 meses. A DL_{CO} esteve correlacionada com RBC: TP (r = 0,60, IC 95% = 0,22 a 0,82, p = 0,004) aos 7 meses. Embora as medições de DL_{CO} e SGRQ tivessem melhorado, estes valores não normalizaram 14 meses após a infecção. Ensaio Clínico. Gov NCT04584671.

INTRODUCTION

In patients with postacute COVID-19 syndrome (PACS), fatigue, chest pain, brain fog and dyspnoea are common and contribute to poor quality of life (QoL).^{1,2} Recent studies showed that 7%–30%^{1,3} of people with PACS remain symptomatic 1–6 months postinfection. Unfortunately, the underlying mechanisms and pathologies responsible for PACS are not well understood.

Chest CT measurements of abnormal pulmonary vascular blood distribution⁴ and fibrosis⁵ have been reported in patients following recovery from COVID-19 infection. Hyperpolarised ¹²⁹Xe MRI has also revealed alveolar gas-transfer abnormalities in PACS,^{6,7} including in never-hospitalised people up to 41 weeks postinfection.⁸ However, longitudinal ¹²⁹Xe measurements have not been reported and previous studies did not have access to pre-COVID-19 imaging to inform on potential mechanisms linking symptoms and gas-exchange abnormalities.^{7,8} Here, we endeavoured to determine whether ¹²⁹Xe MRI gas-transfer measurements normalised over time in people with PACS and if such changes occurred in concert with improved QoL and DL_{CO} measurements.

METHODS

We obtained written-informed consent from participants 18–80 years of age for this prospective study. Participants with a previous positive PCR COVID-19 test and ongoing symptoms were recruited from a local COVID-19 clinic. Study

visits were planned for 3±1 months (baseline) and 15±3 months (follow-up) post-COVID-19+ test. Participants underwent ¹²⁹Xe ventilation MRI, ¹²⁹Xe gas-transfer MRI, spirometry, diffusing capacity of the lung (DL_{CO}) measurement, fraction of exhaled nitric oxide (FeNO) measurement, 6 min walk test (6MWT) and the St. George's Respiratory Questionnaire (SGRQ). The ¹²⁹Xe MRI red blood cell (RBC) to alveolar tissue plasma (TP) ratio was the primary endpoint. SPSS (SPSS Statistics V.27.0; IBM) was used for all statistical analyses. Data were tested for normality using Shapiro-Wilk tests and nonparametric tests were performed for non-normally distributed data. Correlations were evaluated using Pearson (r) and Spearman (ρ) correlations. Pearson and Spearman correlations at baseline and follow-up were compared using the Fisher's z-score. Repeated measures were tested using paired t-tests. Results were considered statistically significant when the probability of making a type I error was <5% (p<0.05). Detailed methods are provided in online supplemental file 1. Baseline results were previously reported.⁸

RESULTS

At baseline, we enrolled 34 participants⁸ and 21 of these (7 female, age=56±15 years) returned for follow-up. For these 21 participants with PACS, the baseline visit occurred 7±4 months post-COVID-19 infection with positive tests occurring during the period March 2020 to April 2021, which was prior to the population-based vaccination initiatives in our local area. The follow-up visit occurred 14±4 months post-COVID-19 infection. Participant demographics are detailed in online supplemental e-Table 1. Nine of these participants were hospitalised due to COVID-19 infection, and one required intubation during a 4-week intensive care unit admission. Five participants were diagnosed with pulmonary embolism (via CT angiogram) during their COVID-19 infectious period. Medications are summarised in online supplemental e-Table 2.

Figure 1 summarises baseline and follow-up clinical, QoL and imaging measurements in tabular format and spaghetti plots for DL_{CO}, SGRQ and ¹²⁹Xe MRI measurements. There were no significant differences in spirometry, 6MWD (Δ=22; 95% CI=0 to 44, p=0.084) and FeNO (Δ=-3; 95% CI=-6 to -1, p=0.084) between visits; FeNO measurements were normal across visits. DL_{CO} (Δ=14; 95% CI=7 to -21, p<0.001), SGRQ-total (Δ=-6; 95% CI=-1 to -11, p=0.044) and symptom-score (Δ=-11; 95% CI=-2 to 20, p=0.032) significantly improved at follow-up. There was also significantly improved



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A

	Baseline (n=21)	Follow-up (n=21)	Difference [95% CI]	Significance (p)
Days Since +	198 (131)	420 (120)	222 [199,245]	
FEV ₁ % _{pred}	92 (22)	92 (22)	-0.4 [-2.8,2]	.729
FVC % _{pred}	91 (21)	93 (27)	3 [-5.2,11.2]	.555
FEV ₁ /FVC %	78 (11)	78 (13)	-0.4 [-4.4,3.6]	.888
FeNO	24 (16)*	21 (15)*	-3 [-6,-1]	.084
DL _{CO} % _{pred}	81 (20)*	96 (23)*	14 [7,21]	<.001
Quality-of-Life				
SGRQ	33 (20)	27 (21)	-6 [-11,-1]	.044
Symptom	42 (23)	31 (26)	-11 [-20,-2]	.032
6MWD m	409 (75)	431 (88)	22 [0,44]	.079
mBDS post-exertion	2.0 (1.5)	1.5 (1.8)	-0.7 [-1.0,-0.4]	.019
¹²⁹Xe MRI				
VDP	5 (9)*	4 (9)*	-0.3 [-1.2,0.6]	.500
RBC:TP	0.32 (0.09)	0.35 (0.09)	0.03 [0.01,0.05]	.051
TP:gas	1.11 (0.28)	1.13 (0.26)	0.02 [-0.06,0.05]	.659
RBC:gas	0.35 (0.14)	0.40 (0.16)	0.05 [0.01,0.09]	.055

B

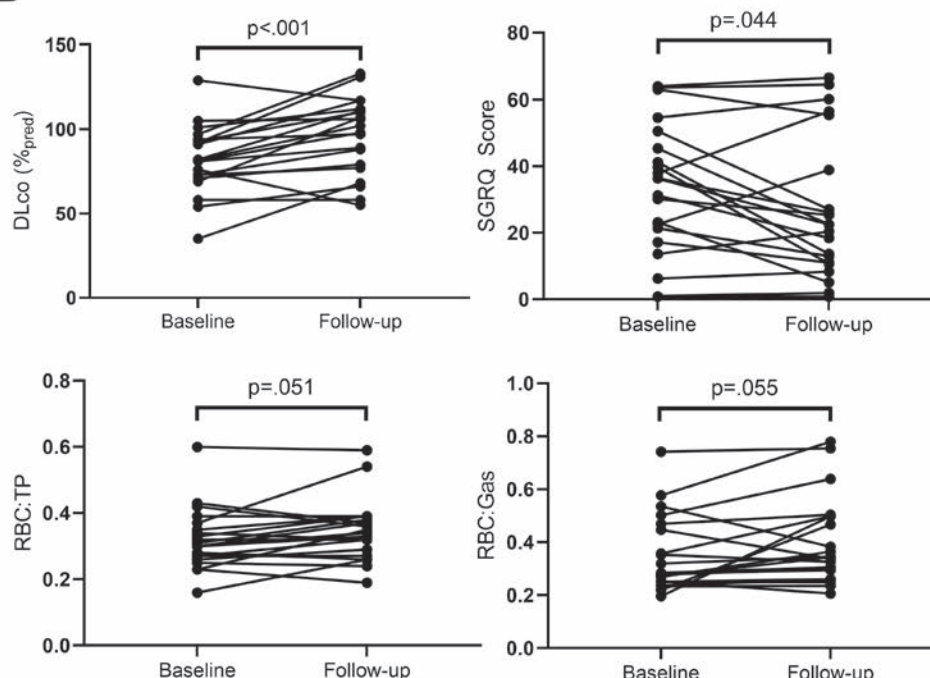


Figure 1 Clinical, quality of life and imaging measurements at baseline (7±4 months since PCR test) and follow-up (14±4 months since PCR test). (A) shows tabulated baseline and follow-up measurements. (B) provides spaghetti plots for DL_{CO}, SGRQ score, ¹²⁹Xe MRI RBC:TP and RBC:gas measurements at baseline and follow-up. Differences were analysed for significance using paired t-tests. *n=20. 6MWD, 6 min walk distance; DL_{CO}, diffusing capacity of the lung for carbon monoxide; FEV₁, forced expiratory volume in 1 s; %_{pred}, per cent of predicted value; FVC, forced vital capacity; FeNO, fractional exhaled nitric oxide; mBDS, modified Borg Dyspnoea Scale; RBC, red blood cell; SGRQ, St. George's Respiratory Questionnaire; TP, tissue plasma.

postexertional dyspnoea (measured using the modified Borg Dyspnoea Scale post-6MWT, $\Delta = -0.7$; 95% CI = -0.2 to -1.2, $p = 0.019$) but not ¹²⁹Xe RBC:TP ($\Delta = 0.03$; 95% CI = 0.01 to 0.05, $p = 0.051$), ¹²⁹Xe RBC:gas ($\Delta = 0.06$; 95% CI = 0.02 to 0.10, $p = 0.055$) or FeNO ($\Delta = -3$; 95% CI = 0 to -6, $p = 0.084$) at 14 months. At baseline, two participants desaturated ($\Delta \text{SpO}_2 = -9\%$, -7%) following the 6MWT while at follow-up, no participants desaturated.

Figure 2 shows representative three-dimensional ¹²⁹Xe MRI RBC maps coregistered with the corresponding segmented CT vessel tree for a single 31-year-old male participant at baseline and follow-up. ¹²⁹Xe MRI RBC map focal defects were obvious in the left and right lower lobes at baseline (shown in the insets) and this was coincident with an SGRQ total score of 23, postexertional breathlessness score of 3 and RBC:TP ratio of 0.37. At follow-up, shown in the right panel, the RBC defects visually improved and

this was coincident with clinically relevant improvements in SGRQ total score of 5, postexertional breathlessness score of 1 and improved RBC:TP ratio (0.54). Online supplemental e-Figure 1 shows multiple slices of ventilation and two dimensional raw RBC component of the dissolved phase images at both baseline and follow-up for additional participants.

Figure 3A shows weak-to-moderate correlations for DL_{CO} and ¹²⁹Xe MRI RBC:TP ($r = 0.60$ 95% CI = 0.22 to 0.82, $p = 0.004$) and RBC:Gas ($\rho = 0.48$, 95% CI = 0.04 to 0.76, $p = 0.029$) at baseline. Figure 3B shows DL_{CO} correlations at follow-up (RBC:TP $r = 0.47$, 95% CI = 0.04 to 0.76, $p = 0.035$; RBC:Gas, $\rho = 0.57$, 95% CI = 0.16 to 0.81, $p = 0.009$). The correlations for DL_{CO} and RBC:TP at baseline ($r = 0.60$, $p = 0.004$) and follow-up ($r = 0.47$, $p = 0.03$) were not significantly different (z score = 0.51, $p = 0.609$). Online supplemental e-Figure 2 shows significant correlations for the change in SGRQ at follow-up with the change in DL_{CO} ($r = -0.55$, CI = -0.14 to -0.80,

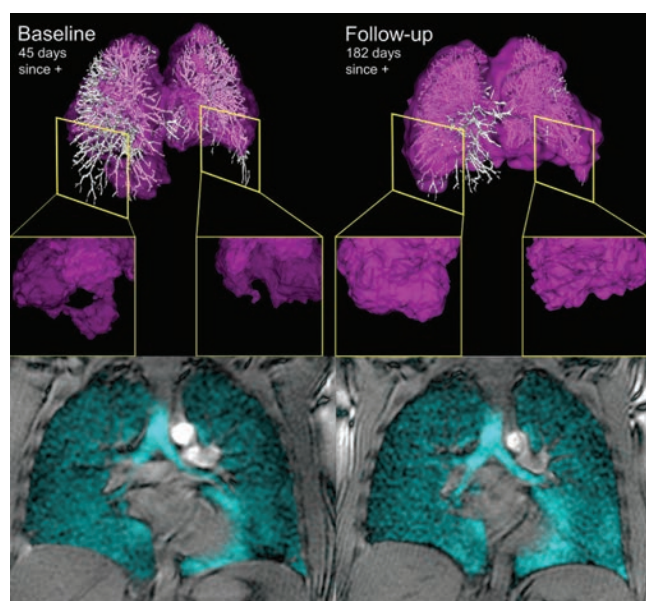


Figure 2 ^{129}Xe MRI and coregistered pulmonary vascular tree CT at baseline and follow-up. Left and right panels show ^{129}Xe MRI RBC map (pink) coregistered with CT pulmonary vascular tree (white) and bottom panels show ^{129}Xe ventilation images (cyan) for a previously healthy participant hospitalised with COVID-19 symptoms and pulmonary embolism. At baseline, 45 days post-COVID-19 positive test, RBC:TP ratio was abnormally low (0.37) and insets provide examples of RBC map defects. At follow-up the RBC:TP ratio improved (0.54) as did the lower lobe red blood cell map defects shown in the right panel inset. DL_{CO} (baseline=93%pred, follow-up=110%pred) and total SGRQ score. (baseline=23, follow-up=5) also improved at follow-up. DL_{CO} , diffusing capacity of the lung for carbon monoxide; RBC, red blood cell; SGRQ, St George's Respiratory Questionnaire.

$p=0.012$) and postexertional Borg dyspnoea ($r=0.68$, 95% CI=0.35 to 0.86, $p=0.001$).

DISCUSSION

Previous work revealed the presence of ^{129}Xe gas-transfer abnormalities in people with PACS,^{7,8} and showed that these abnormalities were related to dyspnoea and exercise limitation.⁸ We examined a small group of 21 participants with PACS to measure SGRQ, DL_{CO} and ^{129}Xe MRI gas-exchange measurements, 7 months after a baseline visit and observed: (1) significant improvements

in DL_{CO} , SGRQ scores and postexertional dyspnoea, (2) persistently abnormal ^{129}Xe MRI RBC:TP values, (healthy volunteer RBC:TP=0.41±0.10)⁸ and (3) positive correlation for DL_{CO} with ^{129}Xe MRI RBC measurements, negative correlation for the change in DL_{CO} with the change in SGRQ and a positive correlation for the change in DL_{CO} with postexertional dyspnoea at follow-up. Whether this snapshot in time, 14±2 months postinfection reflects a slow, ongoing recovery or permanent impairment, remains to be ascertained.

Previous work⁸ detected a significant correlation between DL_{CO} and ^{129}Xe RBC:TP in PACS and here, we observed that this correlation persisted over time. This suggested that ^{129}Xe RBC:TP detected abnormal alveolar gas-exchange that remained abnormal in people with PACS, long after the infection had resolved. We also observed a correlation between postexertional dyspnoea and DL_{CO} on SGRQ-score, underscoring the impact of dyspnoea and gas-exchange improvements on QoL improvements in PACS.

Together, these data suggest gas-exchange abnormalities at least partially resolved during a period of 7 months (and 14 months postinfection). While we do not know the precise cause of abnormal RBC:TP in these participants, a recently published study that evaluated postmortem COVID-19 lungs described vasculo pathologies including vascular congestion, perivascular inflammation, thromboemboli and infarcts unique to COVID-19 that could explain ongoing pulmonary vascular abnormalities.¹⁰ To our knowledge, this is the first longitudinal ^{129}Xe gas-transfer MRI study of PACS. This study was limited by small sample size. ^{129}Xe spectroscopy had not previously been performed at our site and this study was, therefore, not powered for spectroscopy measurements. The sample size was also limited by incomplete retention of the original cohort of study participants. Retention difficulties stemmed from a number of reasons including the fact that fully recovered participants were less inclined to return for a follow-up visit during the COVID-19 pandemic and because of institutional requirements for fully vaccinated participants at follow-up. We also note that measurements were not available in these participants prior to infection and this makes it difficult to distinguish abnormalities due to PACS or other sources. In particular, seven patients had pre-existing asthma and one had pre-existing COPD, which may have impacted gas-exchange measurements.

We measured improved SGRQ, DL_{CO} and postexertional dyspnoea 14 months as compared with 7 months postinfection. Taken together, these findings provide hypothesis-generating insights, which may help target future research on the mechanisms of gas-exchange abnormalities in people with PACS.

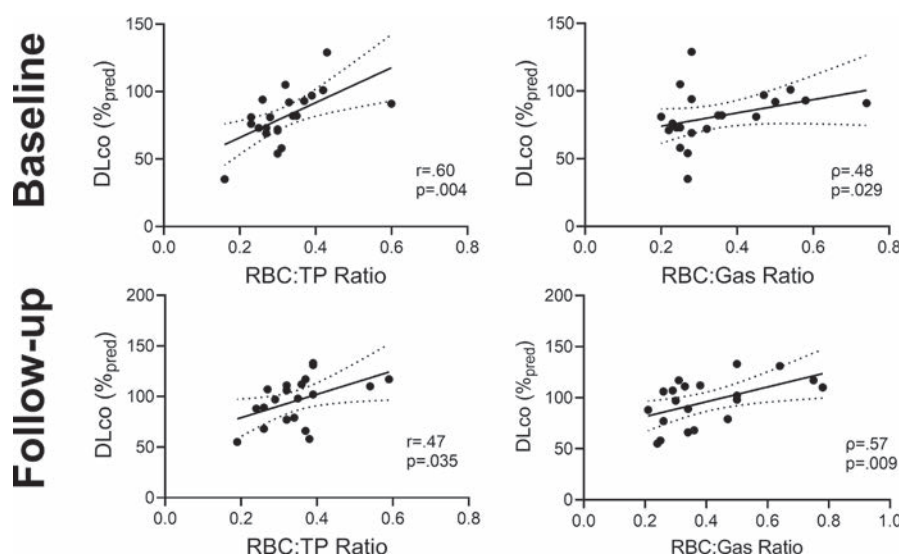


Figure 3 Correlations between DL_{CO} and ^{129}Xe MRI measurements. At baseline and follow-up, there were weak to moderate, significant correlations between DL_{CO} and ^{129}Xe MRI RBC:TP and RBC:gas ratios. (Participants with DL_{CO} measurement $n=20$). DL_{CO} , diffusing capacity of the lung for carbon monoxide; RBC, red blood cell; TP, tissue plasma.

CONCLUSION

In conclusion, our study has shown significantly higher survival in France compared with countries with comparable healthcare systems. France survival estimate exceeded 60 years of age which may be due to differences in availability of transplant for those who need it most.

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Contributors AMM, MJM and HKK were responsible for data acquisition and analysis. AMM was responsible for preparing the first draft of the manuscript. ID and JN were responsible for recruiting study participants and providing clinical input and interpretation of the data. MA, MSA, AO and SS supported the study design development and interpretation of the data. GP was responsible for study design, data analysis and interpretation as well as being the guarantor of study data integrity. All authors had an opportunity to review and revise the manuscript and approved its final submitted version.

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Competing interests SS has received honoraria for speaking engagements from AstraZeneca, Novartis and Polarean, personal fees from Arrowhead Pharma and received study funding from Cyclomedica, none of which was related to this work. JN has received honoraria from AstraZeneca, Horizon Therapeutics and Vertex outside the submitted work. GP has received research support and consulting fees from Novartis and AstraZeneca and personal fees for speaking engagements from AstraZeneca and Polarean Imaging. AMM, MJM, HKK, MA, MSA, ID and AO have no conflicts to declare.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Western University Health Science Research Ethics Board #113224. Participants gave informed consent to participate

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