Short Report

Predicting outcomes following holistic breathlessness services: A pooled analysis of individual patient data

Lisa Jane Brighton[1] (iD), Wei Gao[1], Morag Farquhar[2] (iD), Sara Booth[3],
Sabrina Bajwah[1], William D-C Man[4,5], Charles C Reilly[6], Deokhee Yi[1] (iD),
Irene J Higginson[1] and Matthew Maddocks[1]

Abstract

Background: Holistic breathlessness services have been developed for people with advanced disease and chronic breathlessness, leading to improved psychological aspects of breathlessness and health. The extent to which patient characteristics influence outcomes is unclear.

Aim: To identify patient characteristics predicting outcomes of mastery and distress due to breathlessness following holistic breathlessness services.

Design: Secondary analysis of pooled individual patient data from three clinical trials. Our primary analysis assessed predictors of clinically important improvements in Chronic Respiratory Questionnaire mastery scores (+0.5 point), and our secondary analysis predictors of improvements in Numerical Rating Scale distress due to breathlessness (–1 point). Variables significantly related to improvement in univariate models were considered in separate backwards stepwise logistic regression models.

Participants: The dataset comprised 259 participants (118 female; mean (standard deviation) age 69.2 (10.6) years) with primary diagnoses of chronic obstructive pulmonary disease (49.8%), cancer (34.7%) and interstitial lung disease (10.4%).

Results: Controlling for age, sex and trial, baseline mastery remained the only significant independent predictor of improvement in mastery (odds ratio 0.57, 95% confidence intervals 0.43–0.74; $p < 0.001$), and baseline distress remained the only significant predictor of improvement in distress (odds ratio 1.64; 95% confidence intervals 1.35–2.03; $p < 0.001$). Baseline lung function, breathlessness severity, health status, mild anxiety and depression, and diagnosis did not predict outcomes.

Conclusions: Outcomes of mastery and distress following holistic breathlessness services are influenced by baseline scores for these variables, and not by diagnosis, lung function or health status. Stratifying patients by levels of mastery and/or distress due to breathlessness appears appropriate for clinical trials and services.

Keywords

Breathlessness, advanced disease, treatment outcome

What is already known about the topic?

- Holistic breathlessness services for people with advanced disease and chronic breathlessness can improve psychological aspects of their breathlessness and health.
- Outcomes within and between trials show inconsistencies, which may relate to patient characteristics.

---

[1]Cicely Saunders Institute of Palliative Care, Policy & Rehabilitation, King's College London, London, UK
[2]School of Health Sciences, University of East Anglia, Norwich, UK
[3]Academic Department of Oncology, University of Cambridge, Cambridge, UK
[4]National Heart and Lung Institute, Imperial College London, London, UK
[5]Harefield Pulmonary Rehabilitation Unit, Harefield Hospital, Harefield, UK
[6]King's College Hospital NHS Foundation Trust, London, UK

Corresponding author:
Lisa Jane Brighton, Cicely Saunders Institute of Palliative Care, Policy & Rehabilitation, King's College London, Bessemer Road, London SE5 9PJ, UK.
Email: lisa.brighton@kcl.ac.uk

What this paper adds?

- Baseline mastery and distress due to breathlessness predict outcomes following holistic breathlessness services.
- Diagnosis, lung function and health status do not influence outcomes following holistic breathlessness services.

Implications for practice, theory or policy

- Patients should be considered as candidates for holistic breathlessness services regardless of their diagnosis, lung function and health status.
- Where trials and clinical services face limited resources, prioritising patients with low levels of mastery and/or high levels of distress due to breathlessness appears appropriate.

Introduction

Holistic breathlessness services have been developed for people with advanced disease and chronic breathlessness (i.e. breathlessness that remains persistent despite optimal treatment of the underlying disease[1]). These typically combine input from multiple-specialities (e.g. palliative care, respiratory care) and professions (e.g. medicine, nursing, physiotherapy) to offer comprehensive assessment of patient and carer needs, and tailored pharmacological and non-pharmacological breathlessness management.[2] In chronic respiratory disease, such services represent an evidence-based means for early integration of palliative care based on need rather than prognosis.[3]

Overall, holistic breathlessness services lead to improvements in mastery (i.e. patients' feeling of control over their disease[4]), distress due to breathlessness and psychological health.[2] However, treatment outcomes across and within trials is inconsistent,[2] and the extent to which patient characteristics influence this is unclear. Breathlessness itself is associated with poor physical and mental health,[5] which may influence how patients interact with services. Other factors including health status, exercise capacity, anxiety and depression may also influence outcomes, as they can for pulmonary rehabilitation.[6–9] We aimed to identify patient predictors of outcomes from holistic breathlessness services, focusing on improved mastery and reduced distress due to breathlessness.

Methods

Design

We conducted a secondary analysis of pooled individual patient data from three trials of holistic breathlessness services for patients with advanced malignant and non-malignant conditions, delivered over 2–6 weeks.[10–12] The original data were collected between 2008 and 2012. Our methods built on those in an analysis of patient predictors of response to opioids.[13]

Analysis

Our primary analysis considered improvements on the Chronic Respiratory Questionnaire (CRQ) mastery domain, defined as a 0.5 point increase in line with the minimum clinically important difference.[14] This outcome was measured in all trials and was the primary outcome in the Higginson et al.[10] trial. A secondary analysis considered improvements on Numerical Rating Scale (NRS) distress due to breathlessness (NRS distress), defined as a 1-point reduction.[15] This was the primary outcome in the two Farquhar et al.[11,12] trials but was not measured in the Higginson et al.[10] trial.

Candidate variables (and their reference group/possible score ranges) for the primary and secondary analysis were selected based on availability within the dataset. They included age, sex, diagnosis (reference: COPD), FEV_1 % predicted and baseline scores for CRQ dyspnoea, fatigue, mastery and emotional domains (1–7), EuroQol-5D (EQ5D) Utility Index (−1 to 1) and Visual Analogue Scale (VAS; 0–100), Hospital Anxiety and Depression Scale (HADS) anxiety and depression scores (0–21), and NRS average breathlessness in the previous 24 h (NRS average; 0–10). Baseline NRS distress (0–10) was included only in the secondary analysis. For all variables, the timepoint immediately pre-intervention for each group was treated as 'baseline' (e.g. in the Higginson trial, fast-track participants' baseline was week 1, wait-list participants' baseline was week 6).

Variables significantly related to improvements by the minimum clinically important difference ($p < 0.05$) in univariate logistic regression models were considered in separate multivariate analyses for CRQ mastery and NRS distress. We used backwards stepwise logistic regression modelling, with sequential removal of variables with the largest non-significant ($p > 0.05$) p value in each model. Age, sex (reference: male) and trial (reference: Farquhar et al. 2016) were forced into both models to control for these clinically relevant variables. This secondary analysis of anonymised data did not require ethical approval (references for each contributing study: King's College

Table 1. Sample characteristics.

Variable	Mean (SD)/*n* (%)			
	Higginson et al.[10] 2014	Farquhar et al.[11] 2014	Farquhar et al.[12] 2016	Total
Age	67.0 (9.9)	68.7 (11.5)	72.2 (10.0)	69.2 (10.6)
Female sex	44 (41.9)	40 (60.6)	34 (39.1%)	118 (45.6%)
Diagnosis				
COPD	55 (52.4%)	–	74 (85.1%)	129 (49.8%)
ILD	19 (18.1%)	–	8 (9.2%)	27 (10.4%)
Cancer	22 (21.0%)	67 (100%)	1 (1.1%)	90 (34.7%)
Other	9 (8.6%)	–	4 (4.6%)	13 (5%)
FEV$_1$ % predicted	46.1 (24.2)	–	46.2 (21.4)	46.1 (22.9)
NRS				
Breathlessness (ave. 24 h)[a]	5.99 (2.07)	3.93 (1.96)	4.38 (1.86)	4.89 (2.16)
Distress due to breathlessness[a]	–	4.85 (2.90)	5.21 (2.74)	5.06 (2.80)
HADS				
Anxiety[a]	9.39 (2.90)	7.36 (3.82)	8.20 (4.01)	8.44 (3.64)
Depression[a]	10.36 (2.93)	6.44 (2.79)	7.23 (3.55)	8.24 (3.56)
EQ5D				
VAS	53.3 (17.8)	57.8 (18.5)	54.4 (18.8)	54.8 (18.4)
Utility Index	0.39 (0.32)	0.59 (0.24)	0.50 (0.28)	0.48 (0.29)
CRQ				
Dyspnoea	2.25 (0.81)	3.61 (1.07)	3.25 (0.96)	2.95 (1.09)
Fatigue	2.84 (1.38)	3.30 (1.22)	3.10 (1.08)	3.05 (14.25)
Emotional function	3.72 (1.31)	4.44 (1.06)	4.09 (1.08)	4.03 (1.20)
Mastery	3.54 (1.40)	4.64 (1.17)	4.04 (1.24)	3.99 (1.36)
Improvements by the MCID				
Mastery	36 (51.4%)	17 (34.0%)	44 (59.5%)	97 (50%)
NRS distress	–	36 (69.2%)	45 (58.4%)	81 (62.8%)

COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; NRS: Numerical Rating Scale; HADS: Hospital Anxiety and Depression Scale; EQ5D: EuroQol-5D; CRQ: Chronic Respiratory Questionnaire; MCID: minimum clinically important difference.
[a]Lower scores desirable.

Hospital 10/H0808/17; Cambridgeshire 2 NHS 08/H0308/157).

Results

Participants

The pooled dataset comprised 259 participants (118 female) with a mean (SD) age of 69.2 (10.6) years (Table 1). The most common primary diagnosis was COPD (49.8%), followed by cancer (34.7%) and interstitial lung disease (10.4%).

CRQ mastery

Of the participants for whom CRQ mastery outcomes could be calculated, 97/194 (50%) were classified as improving by the minimum clinically important difference. In univariate analyses, baseline variables significantly associated with improvements in CRQ mastery were baseline CRQ mastery ($p < 0.001$), dyspnoea ($p = 0.008$) and fatigue ($p = 0.009$); EQ5D Utility Index ($p = 0.007$) and VAS ($p = 0.014$); and NRS average ($p = 0.039$). Controlling for age, sex and trial in the multivariate modelling, baseline CRQ mastery remained the only significant predictor of outcomes. Participants with higher CRQ mastery scores at baseline (i.e. better mastery) were less likely to improve by the minimum clinically important difference, with a 43% decrease in odds for a 1-point increase at baseline (odds ratio (OR) 0.57, 95% confidence interval (CI) 0.43–0.74; $p < 0.001$; Table 2).

NRS distress due to breathlessness

Of the participants for whom NRS distress outcomes could be calculated, 81/129 (62.8%) were classified as improving by the minimum clinically important difference. The only variable significantly associated with NRS distress outcomes in the univariate analysis was baseline NRS distress ($p < 0.001$). This remained significant in the multivariate model controlling for age, sex and trial. For every 1-point increase in baseline NRS distress the odds of improving by the minimum clinically important difference increased by 64% (OR 1.64; 95% CI 1.35–2.03; $p < 0.001$; Table 2).

Table 2. Predictors of outcomes in multivariate logistic regression.

Variable	Odds Ratio	(95% Confidence Interval)	p
CRQ mastery improvements by the MCID (n = 188)[b]			
Original study: Farquhar 2014[a]	0.43	(0.19–1.00)	0.05
Original study: Higginson[a]	0.62	(0.29–1.31)	0.21
Age	1.02	(0.99–1.05)	0.13
Female sex	1.68	(0.87–3.24)	0.12
Baseline CRQ mastery	0.57	(0.43–0.74)	<0.001*
NRS distress improvements by the MCID (n = 128)[c]			
Original study: Farquhar 2014[a]	2.40	(0.95–6.09)	0.06
Age	1.03	(0.99–1.07)	0.18
Female sex	2.31	(0.94–5.72)	0.07
Baseline NRS distress	1.64	(1.35–2.03)	<0.001*

CRQ: Chronic Respiratory Questionnaire; NRS: Numerical Rating Scale; MCID: minimum clinically important difference.
[a]Reference: Farquhar 2016.
[b]CRQ mastery model: X2 (5, n = 188) = 31.309, p < 0.001.; AUC = 0.729.
[c]NRS distress model: X2 (4, n = 128) = 39.258, p < 0.001.; AUC = 0.820.
*Significant at p < 0.05.

Discussion

Our findings reveal that baseline CRQ mastery and NRS distress are strong predictors of outcomes from holistic breathlessness services; other patient characteristics we considered, including diagnosis, are not associated with treatment outcome. Clinical services and future trials may therefore consider focusing efforts on patients with poor psychological health relating to their breathlessness, based on screening questions. To illustrate this, in a post hoc analysis of outcomes according to unadjusted baseline CRQ mastery, 75% of patients with a score of ⩽2 improved by the minimum clinically important difference, while just 28% of those with a score of ⩾5 did so. For NRS distress, 89% of patients with a 'severe' score (⩾7) improved by the minimum clinically important difference compared with 39% of those with a 'mild' baseline score (⩽3). With high levels of health service use in breathless patients and limited resources, factors to inform prioritised access to holistic breathlessness services based on likelihood of benefit may be useful.

It is notable that outcomes were not influenced by breathlessness severity, patient diagnosis, lung function, overall health status, anxiety or depression. In some instances, this finding may relate to baseline scores within our sample. For example, baseline scores indicated only mild anxiety and depression;[16] higher levels of psychological distress were therefore not considered within our analyses. However, this finding could also be a product of the tailored nature of these services, whereby individual clinical and demographic characteristics should be addressed.

This work has strengths and limitations. We combined individual patient-level data from three high-quality randomised controlled trials, resulting in a more powerful analysis than would be possible with any single trial. This approach meant our analyses were limited to variables common across the datasets. Potentially important patient factors (e.g. multi-morbidity, functional status) were not tested as they were not measured across all three trials, and fewer cases were available for our secondary analysis around distress. It is also important to acknowledge that there is no consensus on the optimal outcomes of holistic breathlessness services. While we have focused on mastery and distress due to breathlessness, another trial comparing one versus three sessions of a breathlessness service focused on worst breathlessness over the previous 24 h as a primary outcome. Future work may benefit from establishing a core set of clinically relevant patient characteristics and outcomes from breathlessness services, and consistently including these when assessing interventions. Our findings may reflect regression to the mean,[17] however, the magnitude of effects observed and consistent benefit across the controlled trials[2] suggest that this is not the only contributing factor. Finally, these data are limited to holistic breathlessness services trialled in the United Kingdom and may not transfer to international services.

Conclusion

Outcomes of holistic breathlessness services in terms of improved mastery and reduced distress due to breathlessness are influenced by baseline scores for these variables, but not breathlessness severity, patient diagnosis, lung function, overall health status, or mild anxiety or depression. In future trials, and where clinical services face limited resources, selecting or prioritising patients with low levels of mastery or high levels of distress appears appropriate.

Acknowledgements

Data management and sharing

Requests for access to anonymised data should be directed to the corresponding author.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical approval

This secondary analysis of anonymised data did not require ethical approval. Each contributing study obtained appropriate ethical approvals: King's College Hospital 10/H0808/17; Cambridgeshire 2 NHS 08/H0308/157.

Funding

ORCID iDs

Lisa Jane Brighton https://orcid.org/0000-0003-0516-0102
Morag Farquhar https://orcid.org/0000-0001-7991-7679
Deokhee Yi https://orcid.org/0000-0003-4894-1689

References

1. Johnson MJ, Yorke J, Hansen-Flaschen J, et al. Towards an expert consensus to delineate a clinical syndrome of chronic breathlessness. *Eur Respir J* 2017; 49(5): 1602277.
2. Brighton LJ, Miller S, Farquhar M, et al. Holistic services for people with advanced disease and chronic breathlessness: a systematic review and meta-analysis. *Thorax*. Epub ahead of print 29 November 2018. DOI: 10.1136/thoraxjnl-2018-211589.
3. Maddocks M, Lovell N, Booth S, et al. Palliative care and management of troublesome symptoms for people with chronic obstructive pulmonary disease. *Lancet* 2017; 390: 988–1002.
4. Williams JEA, Singh SJ, Sewell L, et al. Development of a self-reported Chronic Respiratory Questionnaire (CRQ-SR). *Thorax* 2001; 56(12): 954–959.
5. Currow DC, Dal Grande E, Ferreira D, et al. Chronic breathlessness associated with poorer physical and mental health-related quality of life (SF-12) across all adult age groups. *Thorax* 2017; 72(12): 1151–1153.
6. Cullen K, Talbot D, Gillmor J, et al. Effect of baseline anxiety and depression symptoms on selected outcomes following pulmonary rehabilitation. *J Cardiopulm Rehabil Prev* 2017; 37(4): 279–282.
7. Mesquita R, Vanfleteren LEGW, Franssen FME, et al. Objectively identified comorbidities in COPD: impact on pulmonary rehabilitation outcomes. *Eur Respir J* 2015; 46(2): 545–548.
8. Reijnders T, Stenzel NM, Schuler M, et al. Disease-specific fear and its relationship with outcomes of pulmonary rehabilitation in COPD. *Eur Respir J* 2017; 50: PA3713.
9. Spruit MA, Augustin IML, Vanfleteren L, et al. Differential response to pulmonary rehabilitation in COPD: multidimensional profiling. *Eur Respir J* 2015; 46(6): 1625–1635.
10. Higginson IJ, Bausewein C, Reilly CC, et al. An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial. *Lancet Respir Med* 2014; 2(12): 979–987.
11. Farquhar MC, Prevost AT, McCrone P, et al. Is a specialist breathlessness service more effective and cost-effective for patients with advanced cancer and their carers than standard care? Findings of a mixed-method randomised controlled trial. *BMC Med* 2014; 12: 194.
12. Farquhar MC, Prevost AT, McCrone P, et al. The clinical and cost effectiveness of a Breathlessness Intervention Service for patients with advanced non-malignant disease and their informal carers: mixed findings of a mixed method randomised controlled trial. *Trials* 2016; 17: 185.
13. Johnson MJ, Bland JM, Oxberry SG, et al. Opioids for chronic refractory breathlessness: patient predictors of beneficial response. *Eur Respir J* 2013; 42(3): 758–766.
14. Schunemann HJ, Puhan M, Goldstein R, et al. Measurement properties and interpretability of the Chronic Respiratory Disease Questionnaire (CRQ). *COPD* 2005; 2(1): 81–89.
15. Ekstrom M, Currow DC and Johnson MJ. Outcome measurement of refractory breathlessness: endpoints and important differences. *Curr Opin Support Palliat Care* 2015; 9(3): 238–243.
16. Stern AF. The hospital anxiety and depression scale. *Occup Med* 2014; 64: 393–394.
17. Linden A. Assessing regression to the mean effects in health care initiatives. *BMC Med Res Methodol* 2013; 13: 119.