Pulmonary rehabilitation and quality of life in alpha-1 antitrypsin deficiency: findings from a retrospective cohort study

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ABSTRACT

Alpha-1 antitrypsin deficiency (AATD) is a rare genetic disorder associated with early-onset chronic obstructive pulmonary disease and impaired quality of life (QoL). This retrospective study evaluated the impact of pulmonary rehabilitation (PR) on QoL using repeated St George's Respiratory Questionnaire (SGRQ) scores. Among 274 patients, PR participants had more severe disease but showed no greater QoL improvement over time. Dyspnoea and exacerbation frequency were the strongest predictors of poorer outcomes. PR was not associated with significantly improved SGRQ trajectories. These findings highlight the need for personalised, disease-specific rehabilitation strategies in AATD to address limitations of conventional PR programmes in this population.

INTRODUCTION

Alpha-1 antitrypsin deficiency (AATD) is a rare genetic condition that predisposes individuals to early-onset chronic obstructive pulmonary disease (COPD), often resulting in airflow limitation, respiratory symptoms and impaired quality of life (QoL).[1 2] Pulmonary rehabilitation (PR) improves dyspnoea, exercise tolerance and QoL in COPD, but its long-term benefits in AATD remain unclear.[3–5]

The St George's Respiratory Questionnaire (SGRQ) is a validated instrument for assessing health-related QoL in chronic lung disease, with higher scores reflecting worse status. In COPD, longitudinal studies have shown that SGRQ scores typically deteriorate over time, largely influenced by lung function decline, dyspnoea severity and exacerbation frequency.[6] In contrast, fewer studies have examined these patterns in AATD. A recent longitudinal study reported stable SGRQ scores over a median 6-year follow-up among individuals with AATD, with baseline symptoms and exacerbations influencing the trajectory.[5] However, that analysis did not evaluate the role of PR in shaping these outcomes.

The current study aimed to assess whether participation in a structured PR programme was associated with changes in QoL over time among individuals with AATD. Using real-world registry data from a national AATD cohort, we examined both cross-sectional and longitudinal patterns in SGRQ total and subscale scores, adjusting for key clinical covariates.

METHODS

Study design and data collection

This retrospective cohort study included patients with AATD seen at Queen Elizabeth Hospital, Birmingham (2016–2023), using data from the Birmingham AATD registry. Patients were grouped according to documented participation in a supervised PR programme, per UK National Health Service criteria. Annual follow-up included lung function tests, exacerbation history, modified Medical Research Council (mMRC) dyspnoea score and QoL assessment using the SGRQ.[6 7] Additional variables included age, sex, genotype and smoking history.

Inclusion criteria

Eligible patients had a confirmed AATD diagnosis with two abnormal alleles (eg, PiZZ, PiSZ or other rare variants; see online supplemental table S1). Only individuals with an mMRC dyspnoea score greater than 1, consistent with PR referral eligibility, were included.[6] At least one SGRQ total score was required for cross-sectional analysis and a minimum of two SGRQ records for longitudinal analysis. Patients without any SGRQ data were excluded.

Statistical analysis

Continuous variable normality was assessed using the Shapiro-Wilk test and visual inspection. Most were non-normally distributed; Mann-Whitney U tests were used. Fisher's exact test was applied to categorical data with small cell counts (<5). Medians and IQRs are reported (online supplemental table S1).

Changes in SGRQ scores were analysed using a linear mixed model among patients with ≥2 records. Fixed effects included forced expiratory volume in 1 s (FEV_1), exacerbation frequency, mMRC score, time since PR, COPD diagnosis and smoking history. A random intercept accounted for repeated measures. Covariates were selected based on clinical relevance, availability within the registry dataset and supporting evidence from prior literature.[4–6] All continuous variables were mean-centred, with multicollinearity excluded (variance inflation factor <1.5). Model assumptions were verified via residual and Q–Q plots (online supplemental figures S2 and S3). Time was modelled continuously. A complete-case approach was used under the missing at random assumption.[8] Analyses were performed in R (V.2024.04.1; Posit

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Table 1 Baseline characteristics (mMRC >1)

Variable	PR (n=189)	Non-PR (n=85)	P value
Age (years)	62 (54, 70)	61 (54, 67)	0.06
Gender (n, %)	Female: 83 (43.9%)	Female: 45 (52.9%)	0.55
Body mass index (kg/m²)	25.72 (22.4, 30.3)	25.71 (23.9, 29.3)	0.33
Phenotype (%)	ZZ: 153 (81%)	ZZ: 62 (72.9%)	*0.02*
Chronic obstructive pulmonary disease diagnosis (n, %)	Yes: 155 (82%)	Yes: 54 (63.5%)	*<0.001*
Smoking history (n, %)	Never: 45 (23.8%)	Never: 20 (23.5%)	0.23
Pack years	16.5 (8.2, 28.0)	11.5 (6.5, 23.5)	0.25
FEV_1 (L)	1.02 (0.80, 1.51)	1.42 (1.01, 1.92)	**0.004**
FEV_1 % predicted	41.96 (33.25, 50.75)	52.70 (45.40, 61.20)	**0.01**
Forced vital capacity (L)	2.94 (2.30, 3.67)	3.30 (2.40, 4.20)	0.16
Oxygen saturation (%)	94 (91, 95)	95 (92, 96)	0.28
Modified Medical Research Council score (n)	2: 65, 3: 81, 4: 43	2: 45, 3: 30, 4: 10	**0.01**
Exacerbation last year	Yes: 133 (70.4%)	Yes: 54 (63.5%)	**<0.001**
Exacerbation frequency	2.0 (1.0, 3.5)	1.0 (0.0, 2.0)	**0.003**
Drinks alcohol (n, %)	Yes: 125 (66.1%)	Yes: 56 (65.9%)	0.80
SGRQ total	59 (46, 73)	61 (40, 76)	0.80
SGRQ symptoms score	75 (57, 89)	74 (53, 83)	0.45
SGRQ impacts score	45.2 (25, 62)	49.0 (27, 65)	0.86
SGRQ activity score	79.7 (66.2, 92.5)	79.1 (56.5, 89.8)	0.19

Baseline characteristics of PR and non-PR groups. Demographic, clinical and quality of life variables for participants with and without PR. Continuous variables are presented as median (Q1, Q3) and categorical variables as n (%). Between-group comparisons were conducted using the Mann-Whitney U test for continuous data and χ^2 or Fisher's exact tests for categorical data. Statistical significance was defined as p<0.05 and is highlighted in bold.
FEV_1, forced expiratory volume in 1 s; mMRC, Modified Medical Research Council; PR, pulmonary rehabilitation; Q1/Q3, first and third quartiles; SGRQ, St. George's Respiratory Questionnaire.

Software, PBC). See online supplemental table S2 for sensitivity analysis.

RESULTS

Baseline analysis

A total of 274 patients were included (189 PR and 85 non-PR). Compared with non-PR participants, PR patients had a higher proportion of PiZZ genotypes (81% vs 72.9%, p=0.02), more COPD diagnoses (82% vs 63.5%, p<0.001) and worse lung function (FEV_1: 1.02 L vs 1.42 L, p=0.004; FEV_1 % predicted: 42% vs 52.7%, p=0.01). They also had higher mMRC scores (median 3 vs 2, p=0.01) and more frequent exacerbations (2 vs 1 event/year, p=0.003). Baseline SGRQ total scores were similar (59 vs 61, p=0.80), as were subscores for symptoms (p=0.45), impacts (p=0.86) and activity (p=0.19) (table 1).

Longitudinal analysis

The analysis included 454 observations from 170 patients with ≥2 SGRQ records. PR participation was not significantly associated with changes in QoL over time (figure 1). Higher mMRC scores were linked to worse QoL (+11.21, p<0.001), while higher FEV_1 was associated with better QoL (–1.85 per L, p=0.048). More frequent exacerbations also predicted worse QoL (+2.51 per event/year, p<0.001). Time since PR showed a modest association with higher SGRQ scores (+1.34/year,

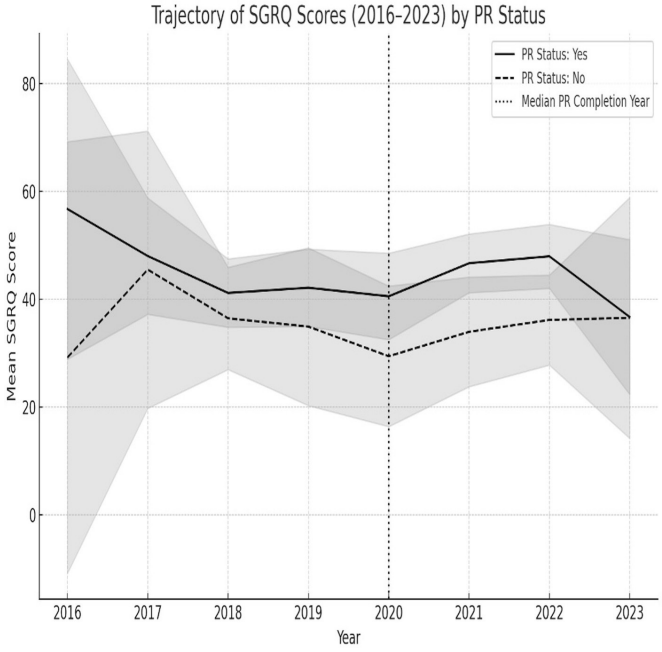

Figure 1 Trajectory of mean SGRQ total scores (2016–2023) by PR status. Solid lines represent patients who completed PR; dashed lines represent those who did not. Shaded areas indicate 95% CIs. The dotted vertical line marks the median year of PR completion. While overall SGRQ scores declined over time in both groups (indicating improved quality of life), the trajectories did not significantly differ by PR status. PR, pulmonary rehabilitation; SGRQ, St George's Respiratory Questionnaire.

p=0.047). Smoking history was borderline significant (p=0.07), and COPD diagnosis was not (p=0.8) (figure 2). Symptoms and impacts domains improved over time, but not in association with PR (online supplemental figure S1).

DISCUSSION

This study examined the impact of PR on QoL in individuals with AATD using repeated SGRQ assessments. Despite greater baseline disease severity, PR participants had similar SGRQ scores to non-PR patients, and no significant QoL improvement over time was observed. These findings suggest that conventional PR may not deliver sustained QoL benefits in AATD, potentially due to differences in disease trajectory or limited programme fit.[3 4] While PR is effective in general COPD populations,[9] AATD-specific adaptations may be necessary to optimise outcomes.[4 5]

mMRC dyspnoea score and exacerbation frequency were the strongest predictors of worsening QoL, while FEV_1 showed a weaker association—supporting prior evidence that lung function alone does not fully capture patient experience.[6] Although improvements in SGRQ symptoms and impacts subscores were observed, these changes were not attributable to PR, echoing findings from longitudinal AATD research.[5]

Limitations include the retrospective design, potential selection bias and absence of detailed PR delivery data. While the SGRQ is validated,[6] it may not fully reflect AATD-specific factors—such as liver-related symptoms, socioeconomic status or genetic implications—which may affect QoL unless explicitly adjusted for in modelling.[10] While the quality of evidence here would not normally support clinical recommendations, we have made suggestions because the rarity of the condition makes

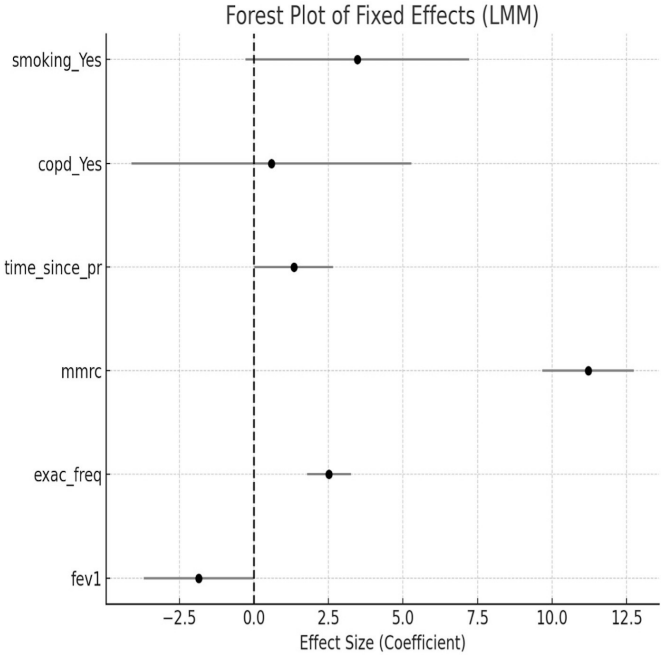

Figure 2 Forest plot of fixed effects from the LMM assessing predictors of St George's Respiratory Questionnaire total scores. Higher dyspnoea severity (mMRC), exacerbation frequency and time since PR were associated with worse QoL (positive coefficients), while higher FEV_1 was associated with better QoL (negative coefficient). Smoking history showed a borderline effect, and COPD diagnosis was not significantly associated. Error bars represent 95% CIs. COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; LMM, linear mixed model; mMRC, modified Medical Research Council; PR, pulmonary rehabilitation; QoL, quality of life.

randomised controlled trials of tailoring rehabilitation within AATD infeasible.

CONCLUSION

Although PR participants had more severe disease at baseline, their QoL trajectories did not differ significantly from non-PR patients. PR was not associated with greater improvement in SGRQ scores. Dyspnoea and exacerbations were key predictors of poorer outcomes, supporting the need for tailored rehabilitation in AATD.

Contributors FA, MN and AMT conceived and designed the study. PRE and JdS contributed to data processing and organisation. AB and AP were involved in data entry and cohort data extraction. FA performed the data analysis and drafted the manuscript. All authors contributed to critical revisions and approved the final version of the manuscript. AMT is the guarantor of the work. Artificial intelligence (AI) tools, including ChatGPT, were used in the preparation of this manuscript to assist with language refinement, grammar checks and improving clarity of writing. AI was specifically used for structuring the text, summarising key findings concisely and ensuring coherence. However, all intellectual contributions, data analysis, interpretation of results and final manuscript revisions were conducted by the authors. The study adheres to ethical research standards, and all content was critically reviewed and approved by the authors before submission.

Competing interests None declared.

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Ethics approval This study involves human participants and was approved by South Central, Oxford C Research Ethics Committee (REC reference 18/SC/0541IRAS, Project ID: 233675). Participants gave informed consent to participate in the study before taking part.

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