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Joint classification of health literacy and inhaler technique and 12-month symptom trajectories in COPD: a prospective cohort study

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Joint classification of health literacy and inhaler technique and 12-month symptom trajectories in COPD: a prospective cohort study

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Abstract

Background Health literacy and inhaler technique are distinct components of chronic obstructive pulmonary disease (COPD) self-management. We investigated the association of their joint classification with 12-month symptom trajectories and clinically meaningful symptom improvement.

Methods This single-centre prospective cohort included 273 patients with stable COPD receiving maintenance inhaled therapy. Adequate health literacy was defined as a 16-item European Health Literacy Survey Questionnaire (HLS-EU-Q16) score ≥12, and good inhalation technique as a seven-item checklist score ≥5. The COPD Assessment Test (CAT) was administered at months 1–6, 8, 10 and 12, yielding 2,457 observations. CAT improvement was defined as the month-1 score minus the month-12 score; a reduction of ≥2 points constituted a clinically meaningful response.

Results The four groups, Q1–Q4, comprised 81, 65, 68 and 59 patients, respectively. Mean CAT improvements were 2.93, 2.32, 1.50 and −0.07 points, and response rates were 76.5%, 63.1%, 52.9% and 37.3% (both $P < 0.001$). Median 12-month exacerbation frequency ranged from 1.00 in Q1 to 2.00 in Q4 ($P < 0.001$). The health literacy–technique interaction was not

statistically significant. The prediction model had an area under the receiver operating characteristic curve of 0.764 (95% CI 0.708–0.819).

Conclusions Joint classification based on health literacy and inhalation technique was associated with differences in symptom trajectories, with the least favourable outcomes observed in patients with both limited health literacy and poor inhalation technique. These findings support further evaluation of joint assessment of health literacy and inhalation technique in patients with COPD.

Keywords COPD; health literacy; inhalation technique; symptom control; inspiratory flow; cohort study

Background

Chronic obstructive pulmonary disease (COPD) requires sustained symptom monitoring and effective use of maintenance inhaled therapy [1]. The effectiveness of inhaled treatment depends partly on correct device use and the integration of treatment instructions into daily self-management. The 2023 Chinese expert consensus identifies individualised device selection and patient training as components of inhalation management [2]. Identifying barriers to treatment understanding and device use is therefore relevant to the organisation of long-term COPD care.

Inhaler errors are common, but their association with clinical outcomes remains incompletely characterised. In the cross-sectional PIFotal study of 1,434 patients with COPD using dry powder inhalers, 81.3% made at least one critical error; specific errors were associated with poorer health status or more frequent severe exacerbations [3]. A 2024 systematic review identified 19 publications examining inhaler errors and COPD outcomes, although most were of low quality and inadequately accounted for adherence [4]. Clinician training and patient education can improve inhaler technique [5,6], but improvements in observed technique do not establish their relationship with subsequent symptom trajectories.

Health literacy encompasses the ability to access, understand, appraise and apply health information and may influence the implementation of treatment advice [7]. In a pooled analysis of five educational studies involving hospitalised patients with asthma or COPD, higher health literacy and more intensive instruction were associated with less metered-dose inhaler misuse after education [8]. A randomised COPD trial of health-literacy-informed follow-up reported fewer hospitalisations and improvements in quality of life and self-management outcomes [9]. A community-based Chinese cluster-randomised trial also found that teach-back education improved COPD Assessment Test (CAT) and psychological symptom scores over 12 months [10].

The longitudinal clinical relevance of joint health literacy and inhaler technique profiles remains uncertain. Cross-sectional associations, post-training assessments and multicomponent educational interventions do not directly establish the symptom trajectories associated with these profiles [3,4,8,9]. Adequate health literacy may coexist with poor technique, whereas patients with limited health literacy may correctly perform inhalation manoeuvres. Assessment of a single domain may therefore overlook clinically relevant differences in self-management needs. Repeated symptom measurements across concordant and discordant profiles can characterise whether between-group differences persist, narrow or widen over time.

This 12-month prospective cohort study investigated whether four groups defined jointly by health literacy and inhaler technique differed in CAT trajectories across nine assessments and in clinically meaningful symptom improvement. Secondary objectives were to compare exacerbation frequency and changes in functional and inhalation measures, assess the health literacy–technique interaction, and explore prediction of clinically meaningful response. Characterising these profiles may inform the design of educational interventions that address treatment understanding, practical device skills or both.

Methods

Study design and population

This single-centre, prospective observational cohort study was conducted in the Department of Respiratory Medicine, The First People's Hospital of Xiaoshan District, Hangzhou, China, between June 2022 and August 2026. The institutional ethics committee approved the study, and participants provided written informed consent.

Patients with physician-diagnosed COPD were screened during inpatient and outpatient encounters. Eligibility required clinically stable disease, maintenance inhaled therapy and the ability to complete the study assessments. Baseline exclusions comprised an exacerbation within the preceding four weeks (n = 61), inability to perform the inspiratory manoeuvre (n = 33) and refusal to participate (n = 24). Of 1,964 patients screened, 512 underwent eligibility assessment and 394 completed enrolment and baseline assessment. During follow-up, 121 patients were excluded: 74 were lost to follow-up, 31 experienced an acute exacerbation or hospitalisation, nine died and seven withdrew consent. The final analytic cohort comprised 273 patients (Additional file 1: Figure S1).

Clinical and functional assessment

Baseline assessments included age, sex, body mass index (BMI), inhaler category and exacerbation frequency during the preceding 12 months. Exacerbations during the subsequent 12 months were recorded separately and defined as acute worsening of respiratory symptoms requiring additional treatment.

The COPD Assessment Test (CAT) comprises eight items scored 0–5, yielding a total of 0–40; higher scores indicate greater COPD-related health impairment [11]. Assessments were conducted at months 1–6, 8, 10 and 12. All 273 patients had complete data at these nine visits, yielding 2,457 observations. Month 1 served as the reference assessment. CAT

improvement was calculated as the month-1 score minus the month-12 score, with positive values indicating improvement. A decrease of ≥2 points defined achievement of the minimal clinically important difference (MCID) [11].

Quantitative inhalation performance was assessed using the PF810 system (Zhejiang E-LinkCare Technology Co., Ltd., China). Measurements at baseline and follow-up included mean effective inspiratory flow (MEIF), inhaled and effective inhaled volume, total and effective inhalation time, and breath-hold duration.

Health literacy was assessed using the 16-item European Health Literacy Survey Questionnaire (HLS-EU-Q16). Responses of "difficult" or "very difficult" were scored 0, and "easy" or "very easy" were scored 1, producing a total of 0–16 [12]. Higher scores indicate greater health literacy. The study-defined threshold was ≥12 for adequate health literacy and <12 for limited health literacy. The distributions of health literacy and technique scores are presented in Additional file 1: Figure S2.

Inhalation technique was assessed by direct observation using a seven-item checklist developed by the investigators on the basis of the seven-step assessment described in the Chinese expert consensus on standard application of inhalation devices in stable chronic airway disease (2019 edition) [13]. The checklist covered preparation, dose loading, exhalation, mouthpiece seal, inhalation, breath-holding, and device closure or repetition. Each correctly performed item was scored 1, and each incorrectly performed or omitted item was scored 0, yielding a total of 0–7. A score of 5 denotes correct completion of five of the seven items. Using the study-defined threshold of ≥5, scores of 5–7 were classified as good technique and scores of 0–4 as poor technique. Item-level scoring criteria are provided in Additional file 1, section A3.

The General Self-Efficacy Scale (GSE) comprises 10 items scored 1–4, yielding a total of 10–40; higher scores indicate greater perceived self-efficacy [14]. GSE scores were analysed

as a continuous variable in regression models and categorised into tertiles for the exploratory interaction plots.

The FRAIL scale includes fatigue, resistance, ambulation, illnesses and weight loss, each scored 0 or 1. Total scores range from 0 to 5, with categories of robust (0), prefrail (1–2) and frail (3–5) [15]. The Short Physical Performance Battery (SPPB) assesses standing balance, usual-pace gait speed and repeated chair stands. Each component is scored 0–4, yielding a total of 0–12; higher scores indicate better physical performance [16].

Anxiety symptoms were assessed using the Generalized Anxiety Disorder-7 scale (GAD-7), which comprises seven items scored 0–3, yielding a total of 0–21; the Chinese-language version has been evaluated in patients with COPD [17]. Depressive symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9), which comprises nine items scored 0–3, yielding a total of 0–27; the Chinese-language version has also been evaluated in patients with COPD [18]. Higher scores indicate greater anxiety and depressive symptom burden, respectively. Both scores were analysed as continuous symptom measures.

Maximal inspiratory and expiratory mouth pressures (MIP and MEP), expressed in cmH_2O, were assessed at baseline only.

For outcomes other than CAT, change was calculated as follow-up minus baseline. Positive changes indicate improvement in HLS-EU-Q16, inhalation technique, GSE and SPPB, whereas negative changes indicate improvement in FRAIL, GAD-7 and PHQ-9. Hand–mouth coordination was assessed separately from the seven-item inhaler technique checklist and dichotomised for analysis as excellent/good versus suboptimal (fair, poor or very poor).

Quadrant definition

Participants were classified into four groups using the study-defined thresholds of HLS-EU-Q16 ≥12 and inhalation technique ≥5. Q1 denotes adequate health literacy and good

technique; Q2, adequate health literacy and poor technique; Q3, limited health literacy and good technique; and Q4, limited health literacy and poor technique. The terms “cognition” and “behaviour” in the figures correspond to health literacy and observed inhalation technique, respectively.

Statistical analysis

Continuous variables were summarised as mean ± SD or median (interquartile range), as appropriate to their distributions, and categorical variables as counts and percentages. Between-group comparisons used one-way ANOVA, Kruskal–Wallis or Pearson chi-square tests, with Tukey adjustment for pairwise comparisons of the primary continuous outcome. The association between health literacy and technique scores was assessed using Spearman rank correlation. A covariate-adjusted two-factor model included health literacy category, inhalation technique category and their interaction; an additive model omitted the interaction term. Multivariable linear regression included month-1 CAT, age, sex, BMI, prior exacerbations, device class, FRAIL, GSE, GAD-7, PHQ-9, SPPB and quadrant membership. Associations are reported as unstandardised regression coefficients (B), expressed in CAT points, with 95% confidence intervals. The two-factor and quadrant models used the same adjustment covariates. Health literacy and technique scores were not entered separately in the quadrant model because they defined group membership.

Longitudinal CAT scores at months 1–6, 8, 10 and 12 were analysed using mixed-effects models with patient-specific effects and time-by-quadrant terms. Linear, quadratic and piecewise time specifications were evaluated, with a knot at month 6 for the piecewise model. Individual and mean CAT trajectories are presented in Additional file 1: Figure S3.

Exploratory prediction analyses used logistic regression and a classification tree. The logistic model included month-1 CAT, FRAIL, GSE and HLS-EU-Q16; discrimination was assessed by the area under the receiver operating characteristic curve (AUC). Patients were grouped

into tertiles of predicted MCID-response probability to compare observed response rates. Diagnostics for the binary MCID-response model are presented in Additional file 1: Figure S4, and exploratory calibration and decision-curve plots in Additional file 1: Figure S5. Tests were two-sided, with $P < 0.05$ indicating statistical significance. Secondary and subgroup analyses were exploratory.

Results

Cohort characteristics and quadrant distribution

The analytic cohort comprised 273 patients with complete CAT assessments at nine visits (2,457 observations). Mean age was 70.7 (SD 9.3) years; 227 patients (83.2%) were men. Mean BMI was 23.6 (SD 3.3) kg/m², and mean month-1 CAT was 11.75 (SD 3.57). Prior-year exacerbation frequency had a median of 1 (IQR 0–4) and a mean of 2.42 (SD 2.90). Q1–Q4 comprised 81 (29.7%), 65 (23.8%), 68 (24.9%) and 59 (21.6%) patients, respectively (Figure 1). Longitudinal CAT profiles are presented in Figure 2.

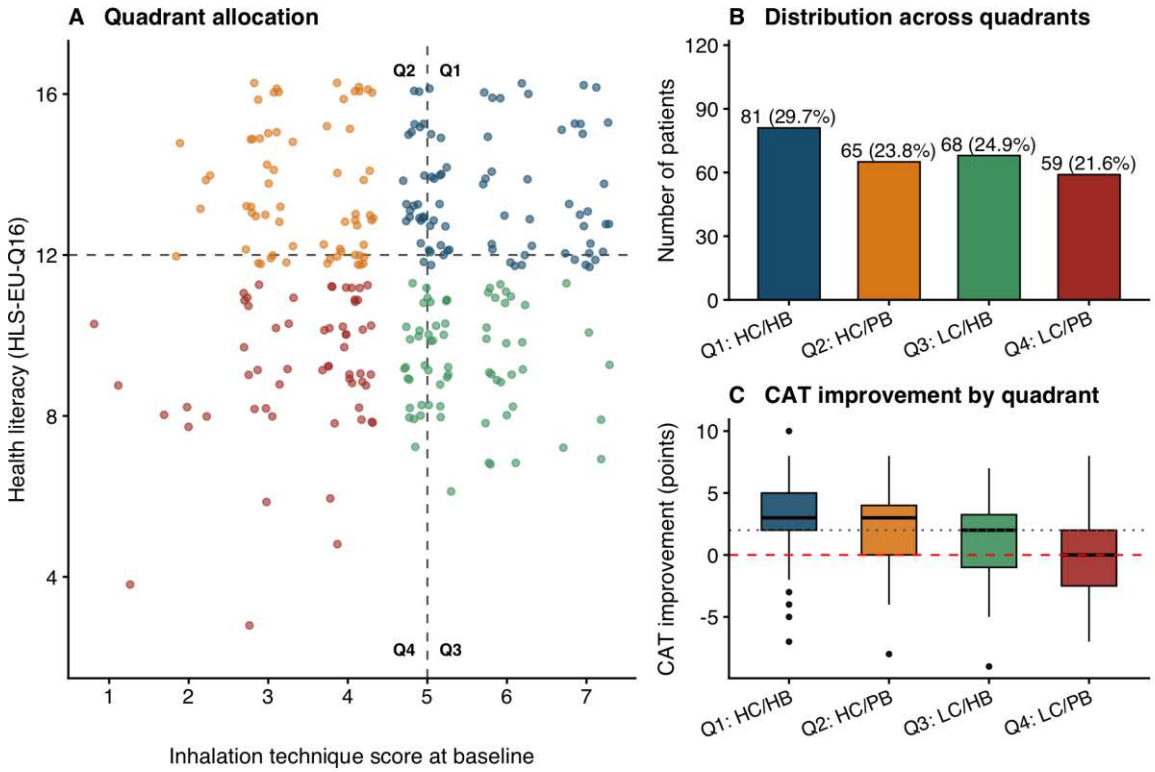


Figure 1. Quadrant allocation, group sizes and CAT improvement. (A) Individual patients plotted by baseline inhalation technique score (x-axis) and health literacy (HLS-EU-Q16, y-axis), with dashed reference lines at technique score 5 and health literacy score 12. Point colour denotes the displayed quadrant assignment. (B) Number and percentage of patients in each quadrant. (C) Box plots of CAT improvement (month-1 minus month-12 CAT) by quadrant, with medians, interquartile ranges, whiskers and outlying observations; the red dashed line is at zero and the grey dotted line is at an improvement of 2 points, the threshold for a clinically meaningful response. Q1, adequate literacy/good technique; Q2, adequate literacy/poor technique; Q3, limited literacy/good technique; Q4, limited literacy/poor technique. CAT, COPD Assessment Test.

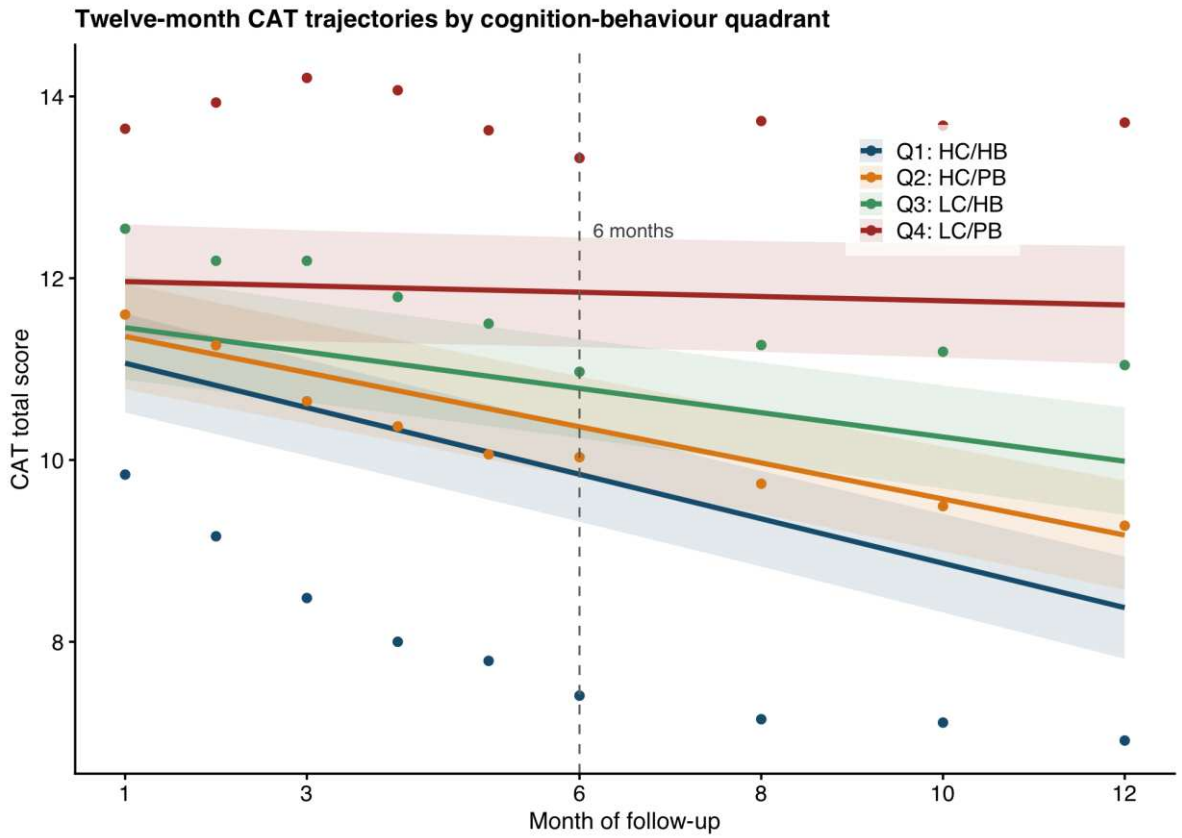


Figure 2. Twelve-month CAT trajectories by quadrant. Solid lines show fitted mean CAT scores from the linear mixed-effects model, and shaded ribbons show 95% confidence bands. Unconnected points show observed quadrant means. The vertical dashed line marks month 6. Observed means are shown at months 1, 2, 3, 4, 5, 6, 8, 10 and 12. Higher CAT scores indicate greater symptom burden.

Mean month-1 CAT ranged from 9.84 ± 2.74 in Q1 to 13.64 ± 2.77 in Q4 ($P < 0.001$; Table 1). Median prior-year exacerbation frequency ranged from 1 (IQR 0–2) in Q1 to 3 (IQR 1–6) in Q4 ($P < 0.001$). GSE ($P < 0.001$), FRAIL ($P = 0.015$), PHQ-9 ($P = 0.012$), SPPB ($P = 0.024$) and inhaled volume ($P = 0.045$) differed across groups. Between-group differences were not statistically significant for age, sex, BMI ($P = 0.227$), device class, GAD-7 ($P = 0.074$), hand–mouth coordination ($P = 0.717$), MIP or MEP. Baseline MEIF also showed no statistically significant between-group difference ($P = 0.415$). The correlation between health literacy and technique scores was weak (Spearman $\rho = 0.03$).

211 **Table 1. Baseline characteristics by health literacy–technique group (N = 273).**

Characteristic	Q1 (n = 81)	Q2 (n = 65)	Q3 (n = 68)	Q4 (n = 59)	P value
Age, years	71.64 ± 9.13	69.78 ± 10.22	71.06 ± 9.97	69.85 ± 7.87	0.568
Sex, male	70 (86.4%)	54 (83.1%)	55 (80.9%)	48 (81.4%)	0.800
BMI, kg/m²	24.02 ± 2.65	23.18 ± 2.91	23.15 ± 3.60	23.99 ± 4.13	0.227
CAT score, month 1	9.84 ± 2.74	11.60 ± 3.69	12.54 ± 3.86	13.64 ± 2.77	<0.001
Exacerbations, prior 12 months	1.00 (0.00–2.00)	2.00 (1.00–4.00)	2.00 (1.00–3.00)	3.00 (1.00–6.00)	<0.001
Device, pMDI/SMI	47 (58.0%)	47 (72.3%)	45 (66.2%)	38 (64.4%)	0.348
Mean effective inspiratory flow, L/min	37.74 ± 15.15	36.34 ± 12.05	33.99 ± 13.83	36.68 ± 13.21	0.415
Inhaled volume, L	1.45 ± 0.51	1.38 ± 0.60	1.24 ± 0.48	1.47 ± 0.54	0.045
Inhalation time, s	2.55 (2.10–3.87)	2.63 (1.95–3.36)	2.67 (1.90–3.69)	2.92 (2.19–3.98)	0.454
Effective inhaled volume, L	1.04 ± 0.55	0.97 ± 0.62	0.87 ± 0.53	1.11 ± 0.67	0.131
Effective inhalation time, s	1.80 ± 1.13	1.66 ± 1.05	1.70 ± 1.21	1.95 ± 1.26	0.500
Breath-hold time, s	1.49 (0.34–10.00)	1.67 (0.40–10.00)	1.10 (0.39–10.00)	1.17 (0.40–10.00)	0.966
Inhalation technique score	5.78 ± 0.85	3.42 ± 0.63	5.53 ± 0.66	3.41 ± 0.83	—
Hand–mouth coordination, excellent/good	38 (46.9%)	32 (49.2%)	27 (39.7%)	27 (45.8%)	0.717
HLS-EU-Q16 score	13.54 ± 1.39	13.63 ± 1.52	9.32 ± 1.34	9.15 ± 1.75	—
General self-efficacy score	32.02 ± 3.41	31.75 ± 3.41	26.31 ± 3.42	25.90 ± 3.64	<0.001

Characteristic	Q1 (n = 81)	Q2 (n = 65)	Q3 (n = 68)	Q4 (n = 59)	P value
FRAIL score	1.10 ± 0.89	1.42 ± 1.06	1.21 ± 0.96	1.58 ± 0.81	0.015
SPPB score	9.07 ± 1.66	8.55 ± 1.48	8.88 ± 1.85	8.25 ± 1.61	0.024
GAD-7 score	3.96 ± 2.66	4.18 ± 2.54	4.31 ± 2.59	5.12 ± 2.79	0.074
PHQ-9 score	4.80 ± 2.93	4.92 ± 3.18	5.46 ± 3.37	6.47 ± 3.23	0.012
MIP, cmH_2O	40.07 ± 19.91	43.02 ± 22.72	41.69 ± 18.35	39.58 ± 16.68	0.738
MEP, cmH_2O	48.69 ± 18.48	51.78 ± 20.01	53.57 ± 21.30	48.34 ± 21.94	0.377

Data are mean ± SD, median (IQR) or n (%). P values were obtained using one-way ANOVA (for normally distributed variables), Kruskal–Wallis (for skewed variables) or Pearson chi-square tests (for categorical variables). Exacerbations in the prior 12 months, inhalation time and breath-hold time were right-skewed and are therefore summarised as median (IQR); other continuous and scale-score variables are summarised as mean ± SD. Group definitions were HLS-EU-Q16 ≥12 for adequate health literacy and an inhalation technique score ≥5 for good technique. CAT values refer to month 1. Q1, adequate literacy/good technique; Q2, adequate/poor; Q3, limited/good; Q4, limited/poor. Hand–mouth coordination was dichotomised as excellent/good versus suboptimal (fair, poor or very poor). Inhalation technique score and HLS-EU-Q16 define the groups and were not compared statistically. Scale-type variables (FRAIL, SPPB, GAD-7, PHQ-9, GSE) were analysed as continuous variables. BMI, body mass index; CAT, COPD Assessment Test; DPI, dry powder inhaler; GAD-7, Generalized Anxiety Disorder-7; GSE, General Self-Efficacy Scale; HLS-EU-Q16, European Health Literacy Survey Questionnaire, 16-item version; IQR, interquartile range; MEIF, mean effective inspiratory flow; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; pMDI, pressurised metered-dose inhaler; SMI, soft mist inhaler; SPPB, Short Physical Performance Battery; SD, standard deviation.

Primary outcome: symptom improvement

Mean CAT improvement was 1.78 points overall and 2.93 (SD 3.07), 2.32 (3.07), 1.50 (3.38) and −0.07 (3.74) points in Q1–Q4, respectively (Table 2). The overall between-group difference was statistically significant ($F(3, 269) = 10.17$, $P < 0.001$; $\eta^2 = 0.102$). The MCID was achieved by 62 (76.5%), 41 (63.1%), 36 (52.9%) and 22 (37.3%), respectively ($P < 0.001$). Unadjusted odds ratios relative to Q1 were 0.52 (95% CI 0.25–1.07), 0.34 (0.17–0.69) and 0.18 (0.09–0.37) for Q2–Q4 (Figure 3). In a two-factor model adjusted for the covariates listed in the Methods, the health literacy term was statistically significant ($F(1, 258) = 5.28$, $P = 0.022$) whereas the technique term was not ($F(1, 258) = 1.72$), and the health literacy–technique interaction was not statistically significant ($F(1, 258) = 0.20$). In the additive model without the interaction term, both terms were statistically significant (health literacy $F(1, 259) = 9.77$, $P = 0.002$; technique $F(1, 259) = 4.63$, $P = 0.032$). Adjusted R^2 values were similar across the quadrant, interaction and additive models (0.307–0.309). Exploratory interaction plots are presented in Figure 4.

Table 2. Month-12 outcomes and changes in scores and inhalation measurements.

Outcome	Q1 (n = 81)	Q2 (n = 65)	Q3 (n = 68)	Q4 (n = 59)	P value
MCID response, n (%)	62 (76.5%)	41 (63.1%)	36 (52.9%)	22 (37.3%)	<0.001
CAT improvement, points (primary)	2.93 ± 3.07	2.32 ± 3.07	1.50 ± 3.38	-0.07 ± 3.74	<0.001
CAT score at month 12	6.91 ± 3.93	9.28 ± 4.63	11.04 ± 5.05	13.71 ± 4.65	<0.001
Exacerbations, 12 months	1.00 (0.00–2.00)	1.00 (0.00–2.00)	1.00 (0.75–3.00)	2.00 (1.00–4.00)	<0.001
MEIF change, L/min	0.00 (−0.70 to 0.80)	0.00 (−0.60 to 0.50)	0.00 (−0.42 to 0.62)	0.00 (−0.55 to 0.40)	0.874

Outcome	Q1 (n = 81)	Q2 (n = 65)	Q3 (n = 68)	Q4 (n = 59)	P value
Inhalation time change, s	0.11 (0.04–0.18)	0.07 (−0.01 to 0.13)	0.09 (0.05–0.17)	0.08 (0.02–0.21)	0.080
Breath-hold time change, s	0.09 (0.00–0.29)	0.07 (0.00–0.32)	0.00 (0.00–0.18)	0.03 (0.00–0.32)	0.275
Technique score change	0.32 ± 0.70	0.38 ± 0.91	0.54 ± 0.76	0.66 ± 0.86	0.064
FRAIL change	-0.07 ± 0.61	-0.09 ± 0.49	-0.22 ± 0.62	-0.27 ± 0.61	0.144
GAD-7 change	-0.49 ± 1.33	-0.54 ± 1.38	-0.37 ± 1.29	-0.78 ± 1.47	0.396
PHQ-9 change	-0.98 ± 1.51	-0.63 ± 1.63	-0.88 ± 1.60	-0.64 ± 1.46	0.458
GSE change	1.06 ± 1.93	1.26 ± 2.11	1.47 ± 1.74	1.56 ± 1.74	0.401
HLS-EU-Q16 change	0.80 ± 0.94	0.49 ± 0.99	0.85 ± 1.08	0.75 ± 1.03	0.170
SPPB change	0.41 ± 0.80	0.32 ± 0.69	0.47 ± 0.84	0.41 ± 0.89	0.772

Data are mean ± SD, median (IQR) or n (%). P values were obtained using one-way ANOVA, Kruskal–Wallis or Pearson chi-square tests. CAT improvement equals month-1 minus month-12 CAT; a decrease of ≥2 points defined a clinically meaningful response (MCID). Other changes equal follow-up minus baseline; increases in technique, HLS-EU-Q16, GSE and SPPB and decreases in FRAIL, GAD-7 and PHQ-9 indicate improvement. Exacerbations and changes in MEIF, inhalation time and breath-hold duration are summarised as median (IQR) and were compared using Kruskal–Wallis tests. One-way ANOVA for CAT improvement: $F(3, 269) = 10.17$, $P < 0.001$; $\eta^2 = 0.102$. Tukey-adjusted comparisons with Q1: Q2 difference -0.60 ($P = 0.692$), Q3 -1.43 ($P = 0.045$), Q4 -2.99 ($P < 0.001$). Groups: HLS-EU-Q16 ≥12 adequate literacy; technique ≥5 good technique. CAT, COPD Assessment Test; GSE, General Self-Efficacy Scale; MCID, minimal clinically important difference; MEIF, mean effective inspiratory flow; SPPB, Short Physical Performance Battery.

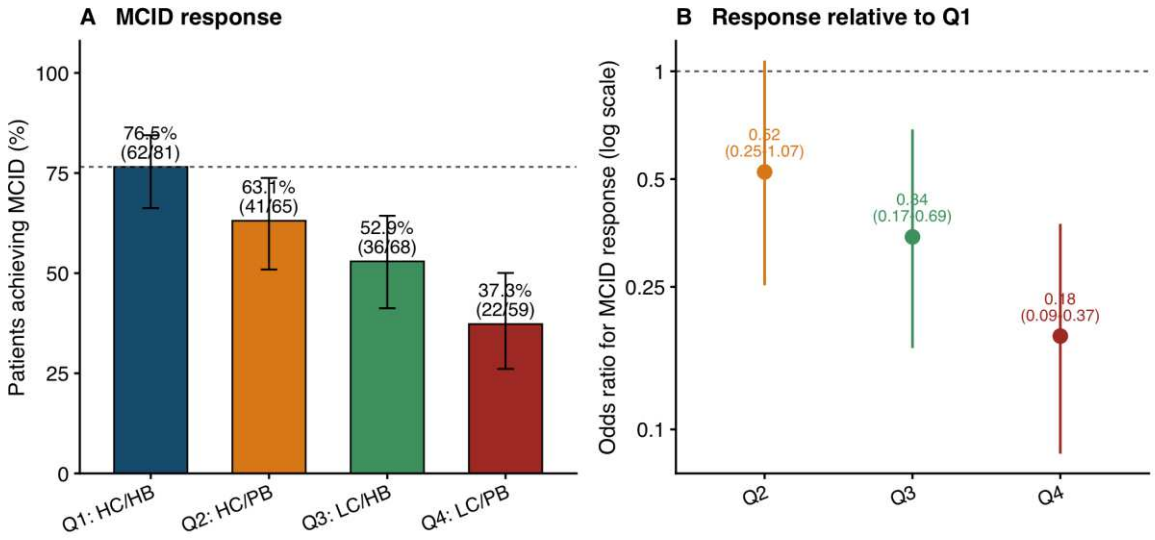


Figure 3. MCID response rates and unadjusted odds ratios by quadrant. (A) Percentages achieving a CAT decrease of at least 2 points: 62 of 81 (76.5%) in Q1, 41 of 65 (63.1%) in Q2, 36 of 68 (52.9%) in Q3 and 22 of 59 (37.3%) in Q4, with 95% confidence intervals; the dashed line indicates the Q1 response rate. (B) Unadjusted odds ratios relative to Q1, with 95% confidence intervals on a logarithmic scale: Q2, 0.52 (0.25–1.07); Q3, 0.34 (0.17–0.69); Q4, 0.18 (0.09–0.37). The dashed reference line is at an odds ratio of 1. CAT, COPD Assessment Test; MCID, minimal clinically important difference.

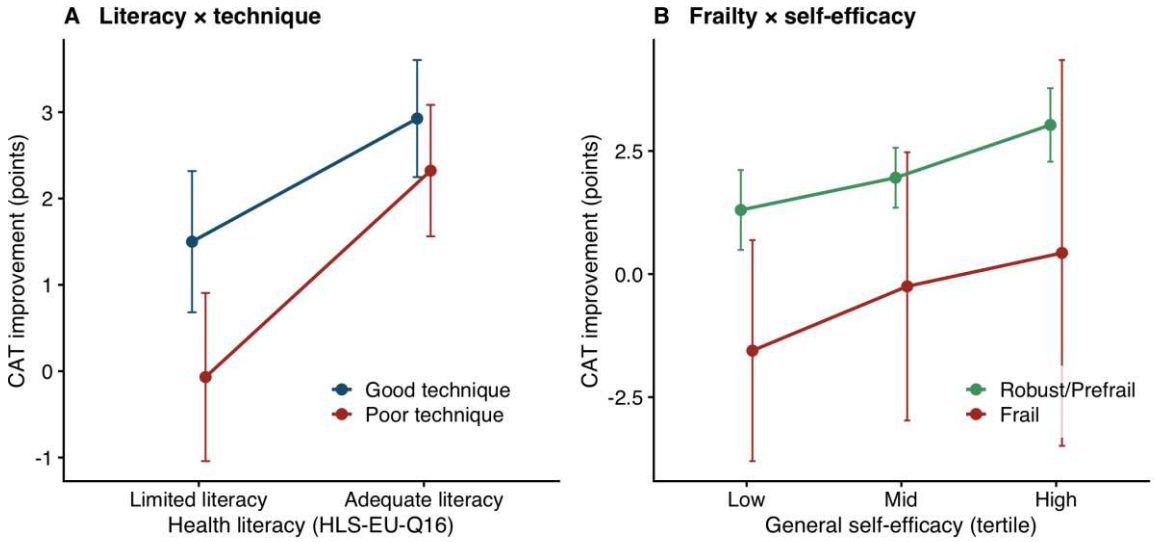


Figure 4. Exploratory interaction plots. (A) Unadjusted mean CAT improvement by health literacy category, stratified by observed inhaler technique. (B) Unadjusted mean CAT

improvement by GSE tertile, stratified as robust/prefrail (FRAIL 0–2) or frail (FRAIL 3–5). Points and error bars represent means and 95% confidence intervals; connecting lines facilitate comparison. CAT improvement equals month-1 minus month-12 CAT.

Secondary outcomes

Median exacerbation counts over 12 months were 1.00 (IQR 0.00–2.00), 1.00 (0.00–2.00), 1.00 (0.75–3.00) and 2.00 (1.00–4.00) in Q1–Q4, respectively ($P < 0.001$; Table 2). Changes in MEIF ($P = 0.874$), inhalation time ($P = 0.080$) and breath-hold duration ($P = 0.275$) did not differ significantly across groups. Mean increases in technique scores were 0.32, 0.38, 0.54 and 0.66 points, respectively ($P = 0.064$). No statistically significant between-group differences were observed in changes in the remaining questionnaire and performance scores (all $P \geq 0.144$).

Adjusted associations with CAT improvement

The multivariable model had an adjusted R^2 of 0.307 ($F(14, 258) = 9.59$, $P < 0.001$; Table 3). Higher month-1 CAT (B = 0.356, 95% CI 0.229–0.483), better SPPB performance (B = 0.414, 95% CI 0.141–0.688) and greater self-efficacy (B = 0.137, 95% CI 0.028–0.245) were associated with greater CAT improvement. Higher FRAIL scores were associated with less improvement (B = −0.834, 95% CI −1.318 to −0.350). Associations with PHQ-9 and GAD-7 were not statistically significant ($P = 0.073$ and 0.128, respectively).

Table 3. Multivariable linear regression of CAT improvement.

Predictor	B	SE	95% CI	P
Intercept	-4.994	3.027	-10.954 to 0.966	0.100
Q2 (vs Q1)	-0.658	0.502	-1.647 to 0.330	0.191
Q3 (vs Q1)	-1.311	0.571	-2.435 to -0.188	0.022
Q4 (vs Q1)	-2.288	0.610	-3.490 to -1.086	<0.001

Predictor	B	SE	95% CI	P
Month-1 CAT score (per point)	0.356	0.065	0.229 to 0.483	<0.001
FRAIL score (per point)	-0.834	0.246	-1.318 to -0.350	<0.001
GSE score (per point)	0.137	0.055	0.028 to 0.245	0.014
SPPB score (per point)	0.414	0.139	0.141 to 0.688	0.003
GAD-7 score (per point)	-0.151	0.099	-0.346 to 0.044	0.128
PHQ-9 score (per point)	-0.146	0.081	-0.305 to 0.014	0.073
Age (per year)	-0.002	0.019	-0.040 to 0.035	0.904
Female sex (vs male)	0.114	0.490	-0.851 to 1.079	0.816
BMI (per kg/m²)	-0.060	0.055	-0.167 to 0.048	0.274
Prior exacerbations (per event)	-0.020	0.076	-0.169 to 0.129	0.789
DPI (vs pMDI/SMI)	0.264	0.379	-0.483 to 1.011	0.487

Values are unstandardised regression coefficients (B), standard errors (SE), 95% confidence intervals and P values from multivariable linear regression. The dependent variable is CAT improvement (month-1 minus month-12 CAT), so positive coefficients indicate greater improvement. Adjusted $R^2 = 0.307$; $F(14, 258) = 9.59$, $P < 0.001$. The joint quadrant effect was assessed using Type III ANOVA: $F(3, 258) = 4.72$, $P = 0.003$. Health literacy and technique scores were not entered as separate covariates because they define quadrant membership. BMI, body mass index; CAT, COPD Assessment Test; DPI, dry powder inhaler; GAD-7, Generalized Anxiety Disorder-7; GSE, General Self-Efficacy Scale; PHQ-9, Patient Health Questionnaire-9; pMDI, pressurised metered-dose inhaler; SMI, soft mist inhaler; SPPB, Short Physical Performance Battery.

Relative to Q1, adjusted coefficients were −0.658 for Q2 (95% CI −1.647 to 0.330; P = 0.191), −1.311 for Q3 (95% CI −2.435 to −0.188; P = 0.022) and −2.288 for Q4 (95% CI −3.490 to −1.086; P < 0.001). Quadrant membership was associated with CAT improvement in the joint test ($F(3, 258) = 4.72$, $P = 0.003$).

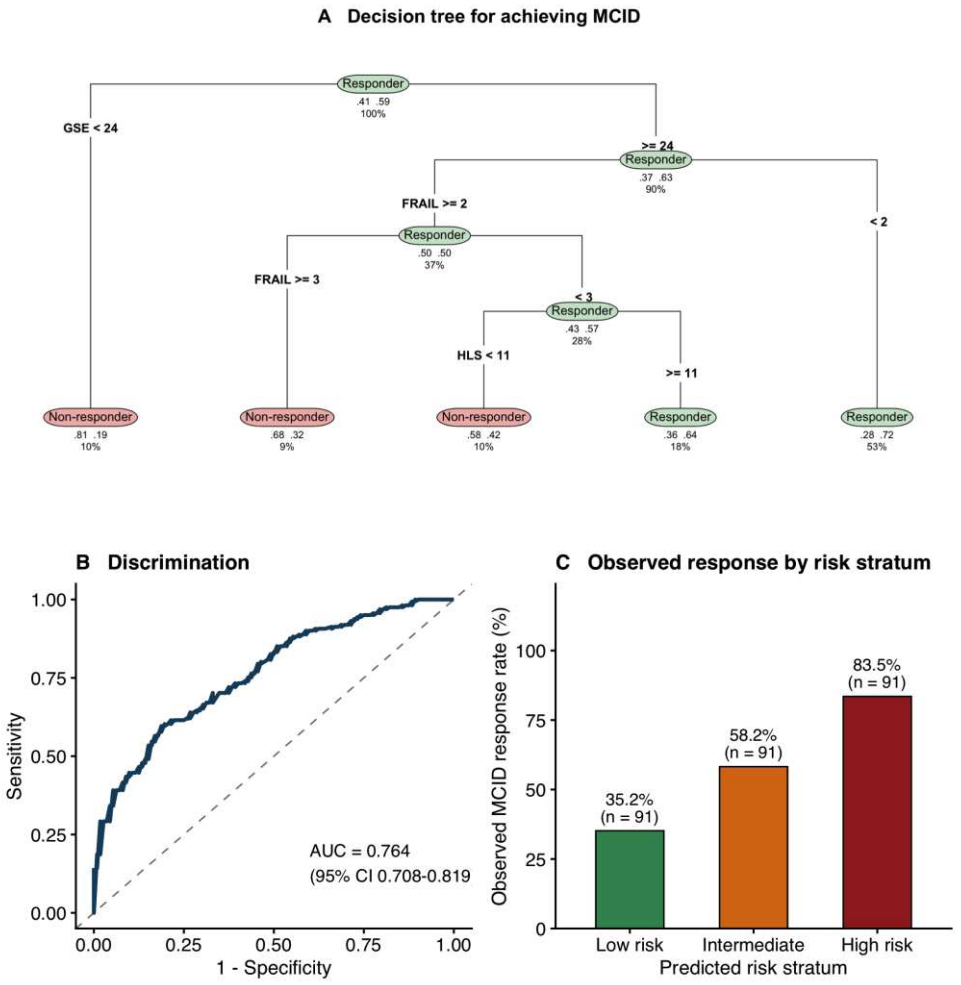
Longitudinal symptom trajectories

CAT scores differed at month 1 and exhibited different longitudinal patterns across groups (Figure 2). Estimated slopes from the linear model, expressed in CAT points per month, were −0.245 (95% CI −0.279 to −0.211) in Q1, −0.199 (−0.251 to −0.147) in Q2, −0.134 (−0.184 to −0.083) in Q3 and −0.023 (−0.076 to 0.030) in Q4. The confidence interval for Q4 included zero; the estimated linear trend in this group was not statistically significant.

Changes in CAT were most pronounced during the first six months and more gradual thereafter (Additional file 1: Figure S3). Adding quadratic time terms improved model fit (likelihood ratio $\chi^2 = 64.38$, df = 4; $P < 0.001$), and all quadrant-by-quadratic-time terms were statistically significant ($P < 0.05$). Q1 exhibited the steepest early decline and the largest quadratic time terms.

Prediction of clinically meaningful response

The logistic model yielded an AUC of 0.764 (95% CI 0.708–0.819) for MCID response (Figure 5B). Group-specific observed outcomes and predicted response probabilities are summarised in Table 4.



316

317 **Figure 5. Exploratory prediction of clinically meaningful CAT response.** (A)

318 Classification tree with splits on GSE, FRAIL and HLS-EU-Q16; nodes show predicted

319 class, non-response/response probabilities and the percentage of patients. (B) ROC curve

320 with AUC 0.764 (95% CI 0.708–0.819); the diagonal indicates chance discrimination. (C)

321 Observed MCID response rates in low, intermediate and high tertiles of predicted MCID-

322 response probability: 35.2%, 58.2% and 83.5%, with 91 patients per stratum. The risk labels

323 in panel C refer to the probability of achieving MCID. GSE, General Self-Efficacy Scale;

324 HLS, HLS-EU-Q16; MCID, minimal clinically important difference; AUC, area under the

325 receiver operating characteristic curve.

Table 4. Observed outcomes and predicted response probabilities by group.

Characteristic	Q1	Q2	Q3	Q4
N	81	65	68	59
MCID response, n (%)	62 (76.5%)	41 (63.1%)	36 (52.9%)	22 (37.3%)
CAT improvement, mean ± SD	2.93 ± 3.07	2.32 ± 3.07	1.50 ± 3.38	-0.07 ± 3.74
Exacerbations, 12 months, mean ± SD	1.15 ± 1.40	1.35 ± 1.42	2.04 ± 2.00	2.51 ± 2.12
FRAIL score, baseline, mean ± SD	1.10 ± 0.89	1.42 ± 1.06	1.21 ± 0.96	1.58 ± 0.81
HLS-EU-Q16 score, baseline, mean ± SD	13.54 ± 1.39	13.63 ± 1.52	9.32 ± 1.34	9.15 ± 1.75
Inhalation technique score, baseline, mean ± SD	5.78 ± 0.85	3.42 ± 0.63	5.53 ± 0.66	3.41 ± 0.83
Predicted MCID response probability	0.69	0.71	0.48	0.44

Values summarise observed outcomes and model-derived probabilities for each group. Predicted probabilities were obtained from a logistic regression model including month-1 CAT score, FRAIL score, GSE score and HLS-EU-Q16 score. Observed response rates by tertile of predicted MCID-response probability are presented in Figure 5C. CAT, COPD Assessment Test; GSE, General Self-Efficacy Scale; MCID, minimal clinically important difference.

Observed response rates were 32 of 91 (35.2%), 53 of 91 (58.2%) and 76 of 91 (83.5%) in the low, intermediate and high tertiles of predicted MCID-response probability, respectively (Figure 5C). The classification tree first split at a GSE score of 24. The 26 patients below this threshold had a response probability of 0.19. Among the 146 patients with a GSE score of 24 or higher and a FRAIL score below 2, the response probability was 0.72. A FRAIL score of 2 defined a further branch (n = 76), within which 26 patients with an HLS-EU-Q16 score

below 11 had a response probability of 0.42 and 50 patients with a score of 11 or higher had a probability of 0.64. The 25 patients with a FRAIL score of 3 or higher had a response probability of 0.32 (Figure 5A).

Discussion

Principal findings

Joint classification of health literacy and inhalation technique identified groups with different symptom trajectories over 12 months. Patients with adequate health literacy and good technique had the greatest mean CAT improvement, whereas those with limited health literacy and poor technique had the least favourable symptom course and the highest follow-up exacerbation frequency. Group-level mean changes nevertheless masked individual variation: 37.3% of patients in Q4 achieved the MCID. These findings support further assessment of both domains when characterising barriers to COPD self-management.

Comparison with previous evidence

The observed differences in outcomes across joint literacy–technique profiles complement previous evidence on inhaler errors and clinical outcomes [3,4]. The present prospective study extends this literature by characterising repeated symptom measurements across combined profiles. Together with evidence on health literacy and inhaler education [7,8], these findings support assessment of both treatment understanding and practical device use.

There was no statistically detectable health literacy–technique interaction for CAT improvement. In the model containing the interaction term, the health literacy term was statistically significant, whereas the technique term was not; both terms were significant in the additive model. These results do not establish a synergistic association between the two domains on the CAT-improvement scale. Q2 and Q3 had intermediate outcomes, and Q4 had the least favourable course. Joint classification characterises complementary self-

management profiles, although its incremental predictive value over either measure alone was not established. Difficulties understanding treatment information and performing inhalation manoeuvres may require different forms of support [5,7,8].

Potential mechanisms and associated factors

Our previous study found that higher MIP was associated with greater mean effective inspiratory flow; however, this association was attenuated after further adjustment for respiratory parameters [19]. The present study extends this line of investigation by examining the longitudinal clinical relevance of joint health literacy and inhaler technique profiles.

Baseline MEIF, MIP and MEP did not differ significantly across groups. These comparisons do not, however, establish that inspiratory performance or respiratory muscle function has no role in the observed symptom differences. MEIF measures average effective inspiratory flow and is distinct from peak inspiratory flow. Errors in device preparation, actuation and inhalation may affect treatment delivery [1,3]. Adherence and pulmonary drug deposition were not quantified, precluding assessment of their contributions to the observed associations.

Frailty and physical performance were associated with CAT improvement after adjustment for the other model covariates. These associations are consistent with prospective evidence linking frailty measures to adverse outcomes in stable COPD [20]. FRAIL and SPPB assess related but distinct domains; recent evidence also supports the reproducibility of physical performance assessment in COPD [16]. These measures may help characterise functional vulnerability alongside health literacy and inhaler technique. The present findings do not establish that good technique mitigates the consequences of frailty.

GAD-7 and PHQ-9 were not significantly associated with CAT improvement in the multivariable model. These findings are specific to the outcome and covariates analysed.

Both instruments quantify psychological symptom burden in patients with COPD [17,18], but their scores do not establish psychiatric diagnoses.

Clinical and research implications

The observed early changes in CAT scores provide a rationale for evaluating reassessment during the initial months of follow-up. Reassessment could combine device demonstration by trained healthcare professionals with patient demonstration and teach-back to identify persistent difficulties in technique or understanding [5,6,10]. The optimal timing and intensity of this support remain to be established.

The four-group classification may inform the content of future educational interventions. For patients with adequate health literacy but poor technique (Q2), educational support could prioritise device demonstration and supervised practice. For those with limited health literacy despite good technique (Q3), it could emphasise clear explanations and support applying treatment information [6,7,8,9]. Patients with both limitations (Q4) may require combined support that also considers functional limitations, psychological symptoms and caregiver involvement.

Controlled studies should evaluate education adapted to health literacy and device coaching separately and in combination to establish whether support tailored to these profiles improves clinical outcomes. Evidence from COPD self-management interventions indicates modest average quality-of-life gains below the threshold for clinical importance and uncertainty about the contribution of individual components [21]. Such trials should therefore assess CAT response and exacerbations alongside changes in knowledge and technique. Objective adherence assessment and device-specific measures of inhalation performance would help clarify potential mechanisms [3,4].

Strengths and limitations

Strengths include prospective follow-up, complete CAT measurements at nine visits within the final analytic cohort, direct observation of inhalation technique, and assessment of complementary functional and inhalation measures. Repeated measurements permitted characterisation of the temporal pattern and persistence of between-group symptom differences.

The single-centre, predominantly male cohort limits generalisability. Unavailable spirometric severity data and unmeasured adherence leave potential residual confounding. Follow-up exclusions, including exacerbation or hospitalisation, may have introduced selection bias and underestimated symptom burden or exacerbation frequency. The literacy and technique thresholds were study-defined, and the equally weighted technique total does not distinguish critical from non-critical errors. Unequal group sizes and multiple secondary comparisons limit precision and increase the possibility of chance findings. Prediction analyses were exploratory and conducted in the study cohort; their generalisability to other populations is unknown. As an observational study, this analysis cannot establish causal mechanisms or the efficacy of targeted interventions.

Conclusions

Joint classification based on health literacy and inhalation technique was associated with differences in symptom trajectories, with the least favourable outcomes observed in patients with both limited health literacy and poor inhalation technique. These findings support further evaluation of joint assessment of health literacy and inhalation technique in patients with COPD.

List of abbreviations

ANOVA, analysis of variance; AUC, area under the receiver operating characteristic curve; B, unstandardised regression coefficient; BMI, body mass index; CAT, COPD Assessment Test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; FRAIL, fatigue, resistance, ambulation, illnesses and loss of weight; GAD-7, Generalized Anxiety Disorder-7; GSE, General Self-Efficacy Scale; HLS-EU-Q16, 16-item European Health Literacy Survey Questionnaire; MCID, minimal clinically important difference; MEIF, mean effective inspiratory flow; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; PHQ-9, Patient Health Questionnaire-9; pMDI, pressurised metered-dose inhaler; ROC, receiver operating characteristic; SD, standard deviation; SE, standard error; SMI, soft mist inhaler; SPPB, Short Physical Performance Battery.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of The First People's Hospital of Xiaoshan District (approval no. Xiaoshan Medical Ethics Approval 2022-Science-072) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Clinical trial number

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The de-identified dataset and the R code used for all analyses are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YZ: conceptualisation, data curation, formal analysis, methodology and project administration.

JW: data curation, formal analysis, investigation, methodology, resources, software, validation and visualisation.

HW: writing—original draft and writing—review and editing.

YS: resources, software, supervision, validation, visualisation, writing—original draft and writing—review and editing.

All authors critically revised the manuscript for important intellectual content, approved the final version and agree to be accountable for all aspects of the work.

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Supplementary information

Additional file 1. Supplementary methods, scoring guide and supplementary figures (.docx). The file contains study and measurement procedures, scoring and statistical details, and Figures S1–S5: study flow; score distributions; individual and mean CAT trajectories; residual and influence diagnostics; and calibration and decision curves.

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