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ORIGINAL RESEARCH

Inhaled Medication Adherence Trajectory and Its Associated Factors in Patients with Chronic Obstructive Pulmonary Disease: A Group-Based Trajectory Modeling

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Objective: This study aims to identify the heterogeneous trajectories of inhaled medication adherence in COPD patients while examining their associated factors and exploring the longitudinal correlation between variables, so as to provide the basis for precise intervention.

Methods: Adopting convenience sampling, chronic obstructive pulmonary disease (COPD) patients hospitalized at The First Affiliated Hospital of Guangzhou Medical University between December 2023 and September 2024 were recruited. General information, Test of the Adherence to Inhalers (TAI; scores of 50 indicate high adherence, 46–49 moderate adherence, and ≤45 low adherence), Chronic Obstructive Pulmonary Disease Knowledge Questionnaire (COPD-Q), Beliefs about Medicines Questionnaire-Specific (BMQ-Specific), Hospital Anxiety and Depression Scale (HADS), and Perceived Social Support Scale (PSSS) were assessed at hospitalization (T0) and 1 month (T1), 3 months (T2), and 6 months (T3) after discharge. The Group-Based Trajectory Model was employed to identify inhaled medication adherence trajectories. Associated factors of trajectories were determined using multinomial logistic regression, and the longitudinal association between variables was explored by the Group-Based Dual Trajectory Model.

Results: A total of 207 patients with COPD completed follow-up. The number and proportion of COPD patients with "medium-low adherence" showed a significant decrease from T0 to T1, followed by an increase from T1 to T3. Trajectories of inhaled medication adherence in COPD patients can be categorised into four classes: "high adherence-persisting group" (50.4%), "medium-low adherence-persisting group" (18.4%), "low adherence rising-persisting group" (15.0%), and "low adherence rising- declining group" (16.3%). Duration of inhalation device use, health literacy, beliefs about medicines, anxiety, and perceived social support were associated factors of trajectories of inhaled medication adherence ($P < 0.05$), with a significant positive correlation between trajectories of inhaled medication adherence and trajectories of beliefs about medicines.

Conclusion: Nearly one-third of COPD patients exhibited poor inhaled medications adherence after discharge, with one month post-discharge serving as a critical turning point. Healthcare providers should prioritize monitoring adherence changes during this period. Four heterogeneous adherence trajectories were identified. Factors influencing each trajectory included: duration of inhaler device use ≤2 years, low level of health literacy, low level of beliefs about medicines, high level of anxiety, and low level of perceived social support. Early screening of these populations and implementation of targeted strategies are essential to enhance precision management.

Keywords: chronic obstructive pulmonary disease, inhaled medication, adherence, group-based trajectory

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Introduction

Chronic obstructive pulmonary disease (COPD) is a common chronic respiratory condition characterised by airway and/or alveolar abnormalities that result in persistent airflow limitation.[1] According to epidemiological surveys, the global prevalence of COPD among people aged 30–79 years was 10.3%.[2] As the third-leading cause of death worldwide,[3] more than 5.4 million patients are expected to die annually from COPD and its related diseases by 2060.[4] A health-augmented macroeconomic modelling study suggested that COPD will cost the world economy $4.326 trillion in 2020−2050.[5] COPD management aims to mitigate both symptoms and future risks.[6] Medication is effective in COPD symptom control—reducing the frequency and severity of acute exacerbations, increasing exercise tolerance, and improving health status.[6] Inhaled medication, which can directly target lung disease sites, has the advantages of high delivery efficiency, high therapeutic indexes, and minimal adverse reactions compared to medications administered through other routes.[7] Based on the abovementioned clinical advantages, inhaled medication has become the first-line treatment for COPD per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendation.[6,8]

Accurately measuring and evaluating inhaled medication adherence in COPD patients remains a significant challenge in clinical practice and research. Currently, prospective assessment of patient adherence primarily relies on two approaches: objective and subjective measurement.[9,10] Objective measurements encompass clinical monitoring (eg, counting doses and reviewing pharmacy dispensing records), electronic system monitoring (eg, electronic inhalation devices, smart inhalers), and biochemical monitoring (eg, measuring drug concentrations or metabolic levels in biological samples such as urine or serum).[9,10] Although objective measurements offer higher accuracy, their widespread adoption is hindered by operational complexity, high costs, or low patient compliance. Subjective measurements include patient self-reporting, questionnaire and scale assessments, and diary methods.[9,10] Subjective measurement methods are widely used clinically due to their simplicity, cost-effectiveness, and ease of administration. Among these, the Test of the Adherence to Inhalers (TAI) is a specific measurement tool designed to assess inhaled medication adherence in COPD and asthma patients, which can identify the types of poor medication adherence in patients and further plan corresponding interventions to correct deficiencies in medication use.[11,12]

Although good medication adherence is key to ensuring favorable treatment outcomes, the current status of inhaled medication adherence in patients with COPD is not ideal, with a systematic review[13] reporting that the non-adherence rate of inhaled medication ranges from 22% to 93% in patients with COPD, and adherence barriers being reported in 30 of the 38 studies it included. The World Health Organization (WHO) considers poor medication adherence as a major threat to health outcomes for people with chronic diseases.[14] Poor inhaled medication adherence was associated with increased hospitalized acute exacerbation rates and costs in patients with COPD,[15] with one study showing that patients who were non-adherent to inhaled medication were almost twice more likely to die compared to adherent ones.[16] Therefore, a comprehensive and scientific assessment of inhaled medication adherence and an analysis of its associated factors are of great clinical value in optimizing the management of the whole course of COPD.

The Chronic Illness Trajectory Model points out that chronic disease pathogenesis is a long and dynamic process, and the psychological, physiological, and spiritual needs of patients are not completely the same at different stages of disease development; the changes in these needs, to some extent, drive the changes in patients' self-management levels.[17] Chen et al[18] demonstrated that medication adherence in patients with chronic diseases was dynamic and varied significantly between groups. In addition, the medication adherence trajectories of patients have a significant impact on their clinical outcomes. Multiple studies have demonstrated that persistent non-adherence and declining adherence were significantly associated with higher healthcare utilization and disease recurrence rates compared to persistent adherence.[19–21] However, most current studies have measured inhaled medication adherence in patients with COPD as a time-fixed variable—although it may change over time—and have not considered group heterogeneity in adherence changes.

Adherence is a multidimensional phenomenon; thus, the WHO has categorized the determinants of medication adherence in patients with chronic diseases into five interacting dimensions: social and economic factors, health care team and system-related factors, condition-related factors, therapy-related factors, and patient-related factors.[14] This classification has some scientific validity and is conducive as it reduces analysis omissions and research biases. Group-based trajectory modeling (GBTM) is a statistical method capable of processing longitudinal data and identifying distinct

developmental trajectories within a population while simultaneously examining the relationships between trajectories and predictive factors or outcomes,[22] which has the advantages of simple operation, few estimated parameters, fast operation speed, low model fitting error rate, and easy interpretation of results.[22] Therefore, this study employed GBTM to explore the developmental trajectory of inhaled medication adherence of patients with COPD within six months after discharge and analyzed the factors associated with the developmental trajectory of inhaled medication adherence of patients with COPD based on the WHO's five-dimensional framework of determinants of medication adherence in chronic diseases while using group-based dual trajectory modeling (GBDTM) to evaluating the longitudinal correlation between adherence and key determinants, so as to help clinical nurses fully understand the changes in inhaled medication adherence of patients with COPD and provide a scientific basis for determining the moment of intervention, formulating appropriate intervention targets for different periods, and implementing corresponding adherence support programs.

Methods

Study Design and Populations

This longitudinal study surveyed patients with COPD who were hospitalized at The First Affiliated Hospital of Guangzhou Medical University between December 2023 and September 2024 using a convenience sampling.

Guidelines for The Diagnosis and Management of COPD (revised version 2021) identified the principle of post-discharge visits for patients with COPD:[8] healthcare professionals should follow up with patients 1–4 weeks after discharge and 12–16 weeks after discharge. Meanwhile, The Chinese Guideline for COPD Management in Primary Care (2024)[23] emphasizes that patients with COPD who have been included in the comprehensive management of chronic diseases should be followed up every 3–6 months. In this study, based on the guideline recommendations, we chose to administer questionnaires to patients with COPD at four moments: during the stabilization of patients' hospitalization (T0), one month after discharge (T1), three months after discharge (T2), and six months after discharge (T3). The reporting of this study adhered to the STROBE checklist.

Study Population Inclusion Criteria

Patients diagnosed with COPD who met the diagnostic criteria of the Guidelines for The Diagnosis and Management of COPD (revised version 2021);[8] age ≥18 years; have been using an inhalation device for more than 3 months;[24] the patient was conscious and able to communicate in writing and verbally.

Study Population Exclusion Criteria

Combined malignancy; history of pneumonectomy or lung transplantation; participation in adherence-related intervention studies during the study period.

Study Population Shedding/Loss to Follow-up Criteria

During the investigation period, if the patient's condition changes and they are unable to cooperate with the investigation or if the patient requests to withdraw, it will be considered as dropout; If three phone calls cannot be made in one follow-up attempt, it will be considered lost to follow-up.

Study Sample Size

The sample size should be ≥200 when using Bayesian information criteria (BIC) as a consideration indicator for the model.[25] Considering a 20–30% loss to follow-up rate, at least 250 patients were eventually included in the study.

Instruments

General Information Questionnaire

This included sociodemographic information (sex, age, education, household income, smoking status, history of occupational dust and biofuel exposure, etc), disease-related information (duration of illness, GOLD grades, COPD-related symptoms, comorbidities, and the number of exacerbations admitted to the hospital in the last year), and

treatment-related information (type of inhalation device, type of inhaled medication, duration of inhalation device use, frequency of inhalation device use, and the need for long-term home oxygen therapy).

COPD-related symptoms were assessed using the COPD Assessment Test (CAT).[26] Each item is scored on a 0–5 scale, with a total score ranging from 0 to 40 and higher scores indicating greater disease impact. Assessment categories were as follows: ≤10 (mild impact), 11–20 (moderate impact), 21–30 (severe impact), and >30 (very severe impact).

Comorbidity status was assessed using the age-adjusted Charlson Comorbidity Index (aCCI).[27] The final score for this scale was calculated based on weighted scores for 19 different diseases and different ages with a total score of 37, with the score varying directly with the number of comorbidities and inversely with the underlying status.

Test of the Adherence to Inhalers (TAI)

The TAI was developed and published by Plaza et al[12] in 2016, specifically for assessing adherence to inhaled medications in patients with COPD and asthma, Chinese scholars Meng et al[24] carried out the Sinicization of the scale. The scale consists of 10 items, including two dimensions, "erratic" and "deliberate." All items of the scale were scored on a 5-point Likert scale with 1 indicating always and 5 indicating never. Based on the total score of the scale, patients were divided into 3 levels of adherence—high (50 points), moderate (46–49 points), and low (≤45 points) adherence. Cronbach's α coefficients for the four measurements of the scale in this study were 0.915, 0.903, 0.921, and 0.922, respectively.

Chronic Obstructive Pulmonary Disease Knowledge Questionnaire (COPD-Q)

This questionnaire was first developed by Paula Maples et al[28] at the Park West Medical Center in the United States and was used domestically after translation and modification by Wang et al[29] The scale consisted of 13 items, with higher scores indicating better health literacy status of patients with COPD. Cronbach's α coefficients for the four measurements of the questionnaire in this study were 0.712, 0.734, 0.736, and 0.744, respectively.

Beliefs About Medicines Questionnaire-Specific (BMQ-Specific)

BMQ-Specific was compiled by Horne et al[30] and Chinese scholars Kang et al[31] carried out the Sinicization of the scale. The scale consists of 10 items, including two dimensions—medication necessity belief and concern belief. BMQ-Specific refers to the belief about inhaled medication in this study. The 5-point Likert scale was used for each item, with scores ranging from 5 to 25 for each dimension and a total score of 50 on the scale, with the score being directly proportional to the strength of the patient's belief in the necessity of medication and inversely proportional to their level of concern. Cronbach's α coefficients measured four times in this study were 0.844, 0.846, 0.854, and 0.872, respectively.

Hospital Anxiety and Depression Scale (HADS)

The HADS was compiled by Zigmond and Snaith[32] and Chinese scholars Zheng et al[33] carried out the Sinicization of the scale. The scale consists of 14 items, with seven items assessing depression (HADS-D) and seven others assessing anxiety (HADS-A). Each item is scored using a 4-point Likert scale. A total score of 0–7 points indicates no anxiety or depression, 8–10 points indicates mild anxiety or depression, and ≥11 points indicates significant anxiety or depression. The higher the score, the more severe the symptoms. Cronbach's α coefficients for the four measurements of HADS-A in this study were 0.723, 0.711, 0.731, and 0.760, respectively; Cronbach's α coefficients for the four measurements of HADS-D were 0.800, 0.832, 0.752, and 0.853, respectively.

Perceived Social Support Scale (PSSS)

The PSSS was compiled by Zimet et al[34] and Chinese scholars Jiang et al[35] performed the Sinicization of the scale. The scale consists of three dimensions: friends, family, and other support, with a total of 12 items on a 7-point Likert scale, with the total score varying from 12 to 84, with 12–36 points indicating low support status, 37–60 points indicating moderate support status, and 61–84 points indicating high support status. Cronbach's α coefficients for the four measurements of the scale in this study were 0.881, 0.865, 0.882, and 0.877, respectively.

Data Collection

During the hospitalization period (T0), researchers conducted face-to-face surveys of patients using paper questionnaires, including the patients' sociodemographic data and clinical data, the patients' inhaled medication adherence, health literacy, beliefs about medicines, anxiety and depression, and social support. The above questionnaires, except sociodemographic data and clinical data, were completed again at one month (T1), three months (T2), and six months (T3) after discharge by the researchers through telephone interviews. The researchers obtained GOLD grades, comorbidities, smoking pack-years, and payment methods for medical expenses from electronic medical records.

The researcher used uniform guidelines and questioning criteria to ensure the truthfulness and accuracy of the information obtained. The researchers chose to conduct the surveys on the patients in a quiet environment to avoid affecting the rest or meals of the participants. Each survey took ≤ 30 minutes to avoid patient fatigue or discomfort, ensuring high-quality questionnaire completion. The questionnaires during the hospitalization of the patients were distributed on the spot, filled out, and recovered in time. The researchers checked for any omissions, missing data, and other issues to ensure the completeness and validity of the questionnaires.

Statistical Analyses

SPSS (version 26.0) and Stata (version 15.0) were used for all statistical analyses. The threshold for statistical significance was set at $p < 0.05$.

Categorical data were described in terms of frequencies and proportions. Continuous variables conforming to a normal distribution were presented as mean values with standard deviations (mean ± SD), whereas non-normally distributed continuous variables were expressed as median values with interquartile ranges M (IQR). The Kolmogorov–Smirnov test was used to assess the normality of continuous variable distribution. Cochran's Q test was used to compare the inhalation medication adherence levels among T0, T1, T2, and T3, with the Bonferroni method being used to correct for significance.

GBTM was used to fit the trajectory of inhaled medication adherence and identify potential subgroups with similar trajectories. The number of GBTM subgroups and the function model of each subgroup were determined according to the following principles:[36–38] (i) The smaller the absolute values of the Akaike Information Criterion and BIC, the better the model fit. (ii) The members of each trajectory group are not less than 5%. (iii) The Average Posterior Probability (AvePP) reflects the degree of conformity of members within a trajectory subgroup to that trajectory. The closer the AvePP is to 1, the better it is, with values of >0.7 being considered the acceptable standard of the model.

The univariate analysis was performed for the factors that might influence the trajectory of inhaled medication adherence of patients with COPD. The χ^2 test or Fisher's exact test was used for categorical variables. The *t*-test or ANOVA was used for normally distributed continuous variables. The Kruskal–Wallis *H*-test or Mann–Whitney *U*-test was used for non-normally distributed continuous variables. The multivariate logistic regression analysis was performed on the factors with statistically significant associations in the univariate analysis ($p < 0.05$) to identify those that independently influenced the heterogeneity of inhaled medication adherence trajectories of patients with COPD.

GBDTM extended from GBTM is a joint model that determines the trajectories of two associated outcomes based on the conditional probability of developing a given outcome. After completing the GBTM for inhaled medication adherence (Variable A) and the statistically significant variable in the multivariate logistic regression analysis (Variable B) separately, they were taken as initial values and fitted to the GBDTM, detailing the degree of association between different levels of trajectory groups for the two variables in the form of a joint probability—the conditional probability of a member of each of Variable B's trajectory groups being a member of each of Variable A's trajectory groups.[39–41]

Ethical Considerations

The research was approved by the Ethics Committee of Guangzhou Medical University (Grant number: 202403019) and written informed consents were obtained from all participants. The study protocol followed the Declaration of Helsinki.

Results

Data Collection Situation

In total, 256 patients were initially included in the study, with 207 of them completing the longitudinal survey. There were 49 cases of loss to follow-up, resulting in a loss-to-follow-up rate of 19.1% (Supplementary Figure 1; S1). There was no statistically significant difference in general features between the 207 patients who completed follow-up and the 49 who were lost follow-up (Supplementary Table 1; S2).

Patients' Baseline Characteristics

The median age of the 256 participants was 65.5 (61.0, 68.8) years. Most participants were male (92.5%), unemployed (86.3%), had attained no more than junior high school education (66.4%), and had a family per capita monthly income of 3000–6000 CNY (50.0%). The disease duration was mainly 5–10 years (53.5%), with 105 cases (41.0%) of GOLD 3 patients. The inhalation device was mainly pMDI (60.5%), and 171 patients (66.8%) received triple therapy. Details are shown in Supplementary Table 2; S3.

Changes in Inhaled Medication Adherence from Hospitalization to Six Months After Discharge

The number and proportion of COPD patients with "medium-low adherence" in T0, T1, T2, and T3 were 86 (41.5%), 51 (24.6%), 65 (31.4%), and 69 (33.3%), respectively. The number and proportion of patients with "incidental non-adherence" in T0, T1, T2, and T3 were 84 (40.6%), 49 (23.7%), 63 (30.4%), and 67 (32.4%), respectively. The number and proportion of patients with "deliberate non-adherence" in T0, T1, T2, and T3 were 78 (37.7%), 47 (22.7%), 59 (28.5%), and 63 (30.4%), respectively.

Cochran's Q test showed a statistically significant difference in the proportion of adherence levels and the proportion of non-adherent behaviors among T0, T1, T2, and T3 ($p < 0.05$). The number and proportion of COPD patients with poor adherence show a trend of first decreasing and then increasing over time. Details are shown in Table 1 and Figure 1.

Identification of the Trajectories of Inhaled Medication Adherence in Patients with COPD

GBTM was employed to identify distinct inhaled medication adherence trajectories. From Class 1 to Class 4, the absolute value of BIC gradually decreases. When the number of classes is 5, the absolute value of BIC increases, and the proportion of the smallest member group is less than 5% (Supplementary Table 3). Therefore, based on the similarity of the model curves, model simplicity, interpretability, and the proportion of the smallest member group, this study determines that 4 classes constitute the optimal model. After determining the optimal number of classes as 4, the polynomial order was progressively reduced until the *P*-value for all group orders was <0.05. Following multiple iterations of polynomial order adjustment, the final polynomial order was established as (0 0 1 3), with statistically significant trajectory results for all groups ($P<0.05$) (Supplementary Table 4; S4a). Based on the optimal polynomial

Table 1 Descriptive Analysis of Inhaled Medication Adherence in COPD Patients at Different Time Points (n=207)

Variables	T0	T1	T2	T3	Q	*p*
Adherence level [n(%)]					43.197	<0.001
High adherence	121(58.5)	156(75.4)*	142(68.6)*	138(66.7)*#		
Medium-low adherence	86(41.5)	51(24.6)*	65(31.4)*	69(33.3)*#		
Types of non-adherent behaviour [n(%)]						
Incidental non-adherence	84(40.6)	49(23.7)*	63(30.4)*	67(32.4)*#	43.702	<0.001
Deliberate non-adherence	78(37.7)	47(22.7)*	59(28.5)*	63(30.4)*#	37.510	<0.001

Notes: Q: Cochran's Q test; *Significantly different compared with T0 ($p<0.05$); #Significantly different compared with T1 ($p<0.05$). Significance has been corrected using the Bonferroni method.

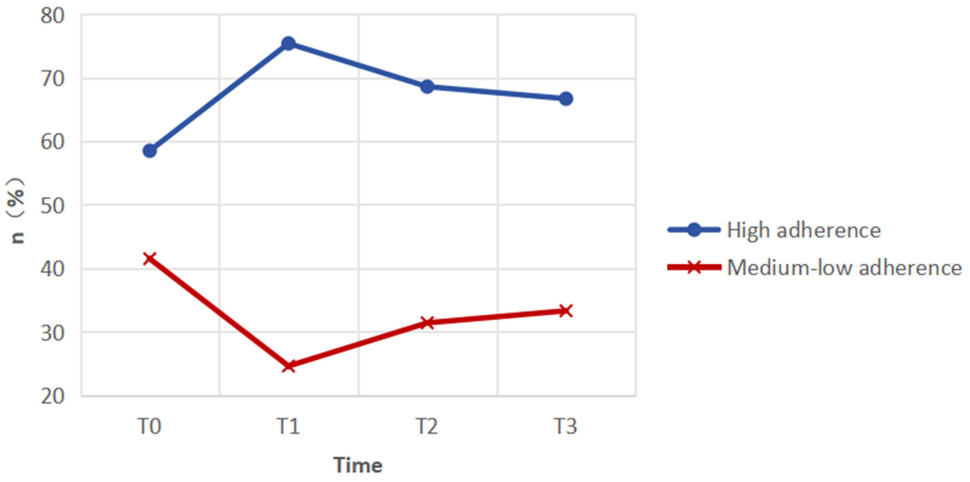

Figure 1 Trend of proportion of inhaled medication adherence level from T0 to T3.

trajectory model, the AvePP was calculated for each class to further clarify the probability that subjects with similar characteristics belong to the same trajectory class. Results showed that the AvePP values for Class 1, 2, 3, and 4 were 0.955, 0.946, 0.934, and 0.966, respectively, all >0.7, indicating good model fit (Supplementary Table 5; S4c).

Based on slope and intercept, we assigned names to the four-class model (details are shown in Figure 2):

① High adherence-persisting group (Class 1). This group had the highest initial adherence, and patients' adherence remained stable over time; thus, the group, which includes 108 patients (50.4%), was named the high adherence-persisting group. ② Medium-low adherence-persisting group (Class 2). In this group, the patients' TAI score consistently fluctuated above and below 45 (the low adherence threshold) and did not change significantly; thus, the group, which contained 37 patients (18.4%), was named the medium-low adherence-persisting group. ③ Low adherence rising-persisting group (Class 3). This group started with low adherence; however, it rose to a high adherence level and remained stable over time; thus, the group, which consisted of 28 patients (15.0%), was named the low adherence rising-persisting group. ④ Low adherence rising-declining group (Class 4). The initial adherence score of this group was the

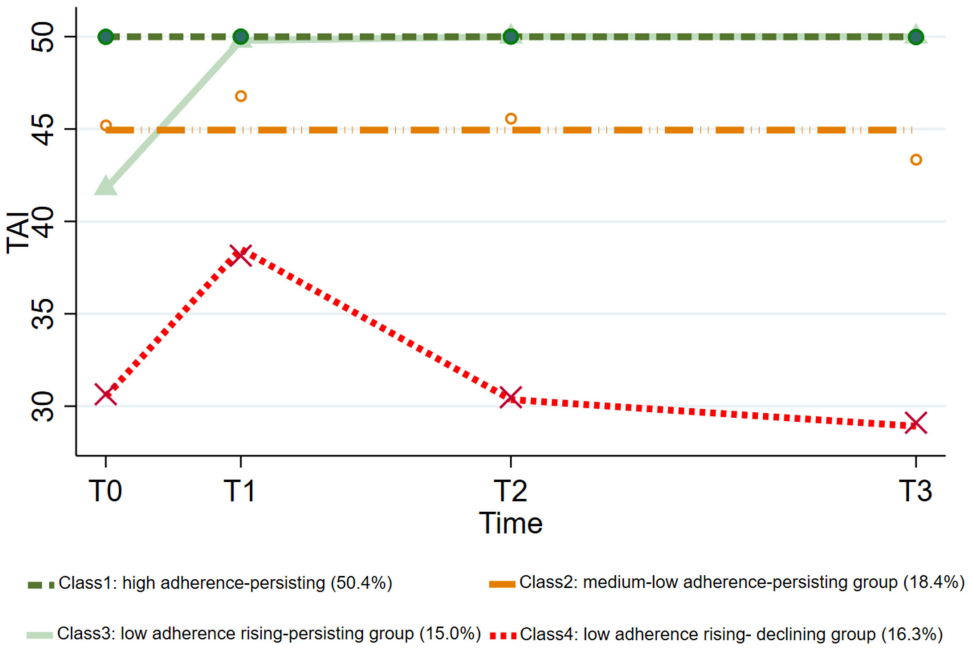

Figure 2 Trajectories of inhaled medication adherence in COPD patients.

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lowest, first increasing and then decreasing; therefore, the group, which contained 34 patients (16.3%), was named the low adherence rising-declining group.

Factors Associated with the Trajectory Heterogeneity of Inhaled Medication Adherence in Patients with COPD

Eight factors that may associate the trajectories of inhaled medication adherence of patients with COPD were identified after the univariate analysis, including disease duration, duration of inhalation device use, long-term home oxygen therapy, COPD-Q score, BMQ-Specific score, HADS-A score, HADS-D score, and PSSS score. ($p < 0.05$). Details are shown in Table 2. A collinearity test was conducted on variables with statistical significance in univariate analysis. Evaluate whether there was significant collinearity between variables by the size of tolerance (TOL) and variance inflation factor (VIF). The test results showed that the TOL values of all variables were >0.1, and the VIF values were <5. The results showed that there was no significant multicollinearity problem among the variables (Supplementary Table 6; S5). To further analyze the associated factors of each inhalation medication adherence trajectory subgroup, a multinomial logistic regression model was employed, with Class 2 and Class 4 serving as the reference group, respectively.

The multinomial logistic regression analysis revealed that compared to Class 4, patients with high levels of health literacy and belief in medicines were more likely to be assigned to Class 1, Class 2, or Class 3. Patients with high levels of anxiety and social support were more likely to be assigned to Class 2; those who had been using a inhaled device for <1 year were less likely to be assigned to Class 1 or Class 3. Compared to Class 2, patients with a high level of beliefs about medicines were more likely to be assigned to Class 1; those with a low level of anxiety were more likely to be

Table 2 Univariate Analysis of Factors Influencing the Trajectories of Inhaled Medication Adherence in Patients with COPD (n=207)

Variables	Categorisation	C1 (n=108)	C2 (n=37)	C3 (n=28)	C4 (n=34)	$\chi^2/H/F$	*p*
Age (year-old)	<60	17 (15.7%)	8 (21.6%)	9 (32.1%)	8 (23.5%)	9.859	0.362
	60~64	27 (25.0%)	11 (29.7%)	6 (21.4%)	7 (20.6%)		
	65~69	45 (41.7%)	17 (45.9%)	8 (28.6%)	13 (38.2%)		
	≥70	19 (17.6%)	1 (2.7%)	5 (17.9%)	6 (17.6%)		
Sex	Male	100 (92.6%)	36 (97.3%)	25 (89.3%)	28 (82.4%)	–	0.155①
	Female	8 (7.4%)	1 (2.7%)	3 (10.7%)	6 (17.6%)		
Residence	Town	64 (59.3%)	17 (45.9%)	16 (57.1%)	13 (38.2%)	5.606	0.132
	Village	44 (40.7%)	20 (54.1%)	12 (42.9%)	21 (61.8%)		
Live alone	Yes	5 (4.6%)	2 (5.4%)	3 (10.7%)	2 (5.9%)	-	0.615①
	No	103 (95.4%)	35 (94.6%)	25 (89.3%)	32 (94.1%)		
Educational background	Primary school and below	30 (27.8%)	9 (24.3%)	10 (35.7%)	12 (35.3%)	3.809	0.702
	Junior high school	39 (36.1%)	12 (32.4%)	9 (32.1%)	14 (41.2%)		
	High school and above	39 (36.1%)	16 (43.2%)	9 (32.1%)	8 (23.5%)		
Occupational status	Employed	12 (11.1%)	7 (18.9%)	4 (14.3%)	6 (17.6%)	–	0.581①
	Unemployed	96 (88.9%)	30 (81.1%)	24 (85.7%)	28 (82.4%)		
Family per capita monthly income	<3000 CNY	36 (33.3%)	16 (43.2%)	12 (42.9%)	16 (47.1%)	–	0.791①
	3000~6000 CNY	58 (53.7%)	18 (48.6%)	14 (50.0%)	15 (44.1%)		
	>6000 CNY	14 (13.0%)	3 (8.1%)	2 (7.1%)	3 (8.8%)		
Payment method for medical expenses	Public expense	0 (0%)	1 (2.7%)	1 (3.6%)	0 (0%)	–	0.071①
	Medical insurance	107 (99.1%)	34 (91.9%)	27 (96.4%)	33 (97.1%)		
	Self-pay	1 (0.9%)	2 (5.4%)	0 (0%)	1 (2.9%)		
Daily use of biofuels or occupational exposure to dust	Yes	14 (13.0%)	3 (8.1%)	6 (21.4%)	7 (20.6%)	–	0.313①
	No	94 (87.0%)	34 (91.9%)	22 (78.6%)	27 (79.4%)		
Smoking status	Never smoker	20 (18.5%)	4 (10.8%)	7 (25.0%)	8 (23.5%)	8.426	0.209

(*Continued*)

Table 2 (Continued).

Variables	Categorisation	C1 (n=108)	C2 (n=37)	C3 (n=28)	C4 (n=34)	χ^2/H/F	p
	Current smoker	18 (16.7%)	7 (18.9%)	9 (32.1%)	9 (26.5%)		
	Ex-smoker	70 (64.8%)	26 (70.3%)	12 (42.9%)	17 (50.0%)		
Smoking index	<400	30 (27.8%)	7 (18.9%)	9 (32.1%)	12 (35.3%)	4.917	0.555
	400~800	50 (46.3%)	22 (59.5%)	10 (35.7%)	14 (41.2%)		
	>800	28 (25.9%)	8 (21.6%)	9 (32.1%)	8 (23.5%)		
Disease duration (years)	<5	23 (21.3%)	11 (29.7%)	14 (50.0%)	14 (41.2%)	15.158	0.019
	5~10	65 (60.2%)	21 (56.8%)	7 (25.0%)	15 (44.1%)		
	>10	20 (18.5%)	5 (13.5%)	7 (25.0%)	5 (14.7%)		
Number of exacerbation admissions within the last year	0	24 (22.2%)	7 (18.9%)	9 (32.1%)	7 (20.6%)	4.761	0.575
	1	51 (47.2%)	23 (62.2%)	11 (39.3%)	18 (52.9%)		
	≥2	33 (30.6%)	7 (18.9%)	8 (28.6%)	9 (26.5%)		
GOLD grades	GOLD 1	2 (1.9%)	1 (2.7%)	0 (0%)	2 (5.9%)	–	0.384①
	GOLD 2	19 (17.6%)	7 (18.9%)	9 (32.1%)	8 (23.5%)		
	GOLD 3	44 (40.7%)	15 (40.5%)	7 (25.0%)	16 (47.1%)		
	GOLD 4	43 (39.8%)	14 (37.8%)	12 (42.9%)	8 (23.5%)		
CAT [M (Q25, Q75)]		25 (22, 29)	22 (19, 29)	22 (18, 29)	25 (18, 27)	5.681	0.128
aCCI [M (Q25, Q75)]		3 (3, 4)	3 (3, 4)	3 (3, 5)	3 (3, 4)	2.371	0.499
Type of Inhaler device	pMDI	68 (63.0%)	27 (73.0%)	15 (53.6%)	15 (44.1%)	–	0.147①
	DPI	39 (36.1%)	10 (27.0%)	12 (42.9%)	18 (52.9%)		
	SMI	1 (0.9%)	0 (0%)	1 (3.6%)	1 (2.9%)		
Type of inhaled medication	LAMA	1 (0.9%)	0 (0%)	1 (3.6%)	1 (2.9%)	–	0.083①
	LAMA-LABA	15 (13.9%)	6 (16.2%)	2 (7.1%)	6 (17.6%)		
	LABA-ICS	16 (14.8%)	2 (5.4%)	7 (25.0%)	10 (29.4%)		
	LAMA-LABA-ICS	76 (70.4%)	29 (78.4%)	18 (64.3%)	17 (50.0%)		
Frequency of inhaler device use	Once a day	27 (25.0%)	10 (27.0%)	5 (17.9%)	10 (29.4%)	1.190	0.755
	Twice a day	81 (75.0%)	27 (73.0%)	23 (82.1%)	24 (70.6%)		
Duration of inhaler device use (years)	<1	13 (12.0%)	9 (24.3%)	3 (10.7%)	18 (52.9%)	40.571	<0.001
	1~2	31 (28.7%)	18 (48.6%)	10 (35.7%)	11 (32.4%)		
	≥3	64 (59.3%)	10 (27.0%)	15 (43.6%)	5 (14.7%)		
Long-term home oxygen therapy	Yes	84 (77.8%)	24 (64.9%)	17 (60.7%)	18 (52.9%)	9.197	0.027
	No	24 (22.2%)	13 (35.1%)	11 (39.3%)	16 (47.1%)		
COPD-Q (Mean±SD)		6.27±2.17	5.49±2.13	5.86±1.98	3.09±1.40	21.401	<0.001
BMQ-Specific[M (Q25, Q75)]		45.00 (42.00, 46.00)	42.00 (37.50, 46.00)	40.00 (30.25, 43.00)	28.00 (23.00, 30.00)	89.271	<0.001
HADS-A [M (Q25, Q75)]		7.00 (7.00, 9.00)	9.00 (8.00, 12.00)	8.00 (7.00, 10.00)	8.00 (7.00, 10.00)	12.089	0.007
HADS-D [M (Q25, Q75)]		7.00 (6.00, 10.00)	9.00 (7.00, 11.00)	9.00 (7.00, 11.00)	10.00 (7.00, 11.00)	11.377	0.010
PSSS (Mean±SD)		55.51±8.58	55.73±8.35	54.46±6.91	47.88±9.62	7.487	<0.001

Notes: C1: high adherence-persisting group; C2: medium-low adherence-persisting group; Cl3: low adherence rising-persisting group; C4: low adherence rising- declining group; χ^2: Chi-square test; H: Kruskal–Wallis *H*-test; *F*: analysis of variance; ①Using Fisher's exact test; smoking index: smoking years × number of cigarettes/day.
Abbreviations: CNY, Chinese Yuan; GOLD, Global Initiative for Chronic Obstructive Lung Disease; pMDI, pressurized metered dose inhaler; DPI, dry powder inhaler; SMI, soft mist inhaler; LAMA, long-acting antagonist; LABA, long-acting β2 receptor agonists; ICS, inhaled corticosteroid; CAT, COPD assessment test; aCCI, age-adjusted Charlson comorbidity index; COPD-Q, chronic obstructive pulmonary disease knowledge questionnaire; BMQ-Specific, beliefs about medicines questionnaire-specific; HADS-A, hospital anxiety and depression scale-anxiety; HADS-D, hospital anxiety and depression scale-depression; PSSS, perceived social support scale.

assigned to Class 1 or Class 3; those who had been using inhaled devices for ≤2 years were less likely to be assigned to Class 1 or Class 3. More details are shown in Table 3.

Longitudinal Associations Between Inhaled Medication Adherence and Variables in Patients with COPD

The multinomial logistic regression showed that COPD-Q score, BMQ-Specific score, HADS-A score, and PSSS score were the factors associated with the trajectory heterogeneity of inhaled medication adherence in patients with COPD.

Table 3 Multifactorial Logistic Regression Analysis of Trajectories of Inhaled Medication Adherence of COPD Patients (n=207)

Groups	Categorisation	β	SE	Wald χ^2	*p*	OR (95% CI)
C1 vs C4[a]						
Intercept		−20.146	5.126	15.445	<0.001	
Duration of inhaler device use (years)	<1	−2.999	1.250	5.752	0.016	0.050 (0.004~0.578)
COPD-Q		0.666	0.315	4.461	0.035	1.947 (1.049~3.613)
BMQ-Specific		0.442	0.088	25.024	<0.001	1.556 (1.309~1.851)
C2 vs C4[a]						
Intercept		−19.810	5.145	14.824	<0.001	
COPD-Q		0.627	0.319	3.867	0.049	1.872 (1.002~3.496)
BMQ-Specific		0.313	0.083	14.066	<0.001	1.367 (1.161~1.610)
PSSS		0.101	0.048	4.350	0.037	1.106 (1.006~1.214)
HADS-A		0.651	0.264	6.074	0.014	1.917 (1.142~3.216)
C3 vs C4[a]						
Intercept		−13.468	4.935	7.447	0.006	
Duration of inhaler device use (years)	<1	−3.697	1.367	7.314	0.007	0.025 (0.002~0.361)
COPD-Q		0.878	0.381	7.609	0.006	2.405 (1.289~4.487)
BMQ-Specific		0.228	0.082	7.744	0.005	1.256 (1.070~1.475)
C1 vs C2[b]						
Intercept		−0.336	2.609	0.017	0.898	
Duration of inhaler device use (years)	<1	−1.539	0.632	5.935	0.015	0.215 (0.062~0.740)
	1~2	−1.220	0.532	5.258	0.022	0.295 (0.104~0.838)
BMQ-Specific		0.130	0.050	6.781	0.009	1.138 (1.033~1.255)
HADS-A		−0.296	0.117	6.383	0.012	0.744 (0.592~0.936)
C3 vs C2[b]						
Intercept		6.342	3.101	4.183	0.041	
Duration of inhaler device use (years)	<1	−2.237	0.993	5.071	0.024	0.107 (0.015~0.748)
	1~2	−1.406	0.707	3.957	0.047	0.245 (0.061~0.980)
HADS-A		−0.355	0.165	4.639	0.031	0.701 (0.507~0.969)

Notes: C1: high adherence-persisting group; C2: medium-low adherence-persisting group; C3: low adherence rising-persisting group; C4: low adherence rising-declining group. The reference group: duration of inhaler device use (years) ≥3. [a]Take C4 as the reference group. [b]Take C2 as the reference group.

Abbreviations: COPD-Q, chronic obstructive pulmonary disease knowledge questionnaire; BMQ-Specific, beliefs about medicines questionnaire-specific; HADS-A, hospital anxiety and depression scale-anxiety; PSSS, perceived social support scale.

Due to the lack of significant changes in patients' health literacy and perceived social support levels over time, trajectories of beliefs about medicines and anxiety were fitted respectively to explore longitudinal associations between inhaled medication adherence and the two variables.

Identification of the Trajectories of Beliefs About Medicines in Patients with COPD

Five models were fitted successively, and the four-class model was found to have the best fitting effect (Supplementary Tables 7–9; S6a–S6c).

Based on the intercept and slope, we named the classes as follows: Class 1 was the low level-declining group, with 22 patients accounting for 10.4%; Class 2 was the low level rising-declining group, with 24 patients accounting for 12.0%; Class 3 was the medium level-rising group, with 57 patients accounting for 25.3%; Class 4 was the high level-persisting group, with 104 patients accounting for 52.3%. Details are shown in Figure 3.

The GBDTM Analysis of Inhaled Medication Adherence and Beliefs About Medicines

Among the patients with beliefs about medicines in the low level-declining group, 86.4% of them belonged to the low adherence rising-declining group. Among patients with beliefs about medicines in the low level rising-declining group, 62.5% of them were in the low adherence rising-declining group. Among patients with beliefs about medicines in the

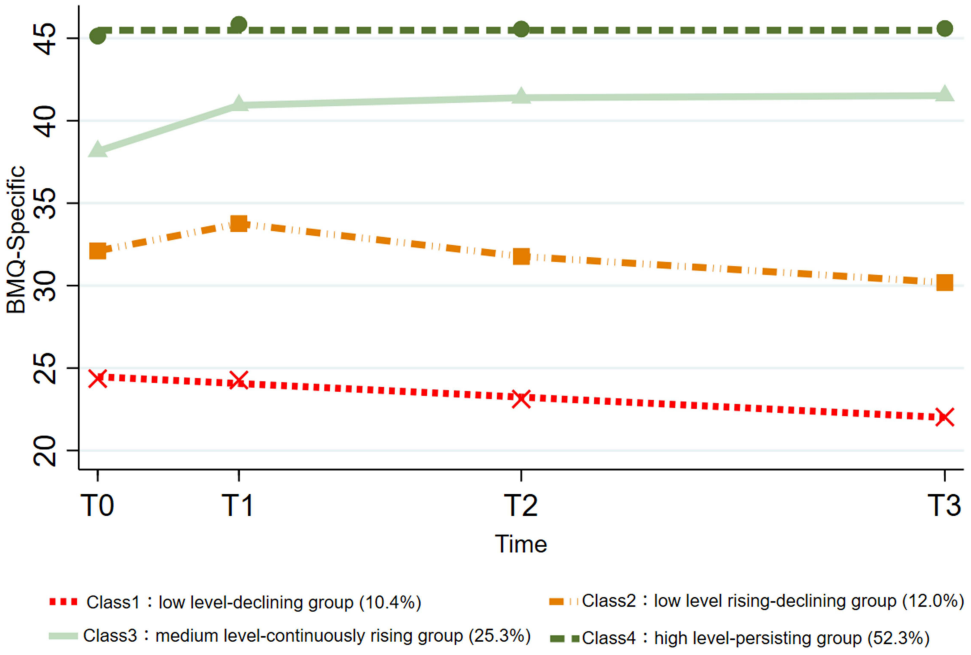

Figure 3 Trajectories of beliefs about medicines in COPD patients.

medium level-rising group, 50.9% of them followed a high adherence-persisting trajectory. Among the patients with beliefs about medicines in the high level-persisting group, 73.1% of them were in the high adherence-persisting group. Thus, there was a positive correlation between the trajectories of inhaled medication adherence and beliefs about medicines in patients with COPD. Details are shown in Table 4.

Identification of the Trajectories of Anxiety in Patients with COPD

We sequentially fitted 1- to 5-class models. Although the 4-class model showed a slight decrease in BIC compared to the 3-class model, it yielded a very small subgroup (3.06% of the sample), leading to unstable parameter estimates and limited clinical significance. In contrast, the 3-class model demonstrated a substantial decrease in BIC and compared with the 2-class model, a trajectory with significant heterogeneity was generated: "persistent high anxiety group". Therefore, we selected the 3-class model as the final solution. Five models were fitted successively, and a significant decrease in the absolute value of BIC was found when fitting the three-class model. Considering the model's interpretability, we chose the three-model although its percentage of the least member group was slightly less than 5%. Details are shown in Supplementary Tables 10–12; S7a–S7c.

Based on the intercept and slope, we named the classes as follows: Class 1 was the low level declining-persisting group, with 128 patients accounting for 61.9%. Class 2 was the medium level-declining group, with 69 patients accounting for 33.3%. Class 3 was the high level-persisting group, with 10 patients accounting for 4.8%. Details are shown in Figure 4.

Table 4 Conditional Probability of Inhaled Medication Adherence Trajectories Based on Beliefs About Medicines Trajectories (%)

Trajectories of Inhaled Medication Adherence	Trajectories of Beliefs About Medicines			
	Low Level-Declining Group	Low Level Rising-Declining Group	Medium Level-Rising Group	High Level-Persisting Group
Low adherence rising-declining group	86.4	62.5	0	0
Low adherence rising-persisting group	0	4.2	24.6	12.5
Medium-low adherence-persisting group	13.6	20.8	24.6	14.4
High adherence-persisting group	0	12.5	50.9	73.1

https://doi.org/10.2147/PPA.S594228

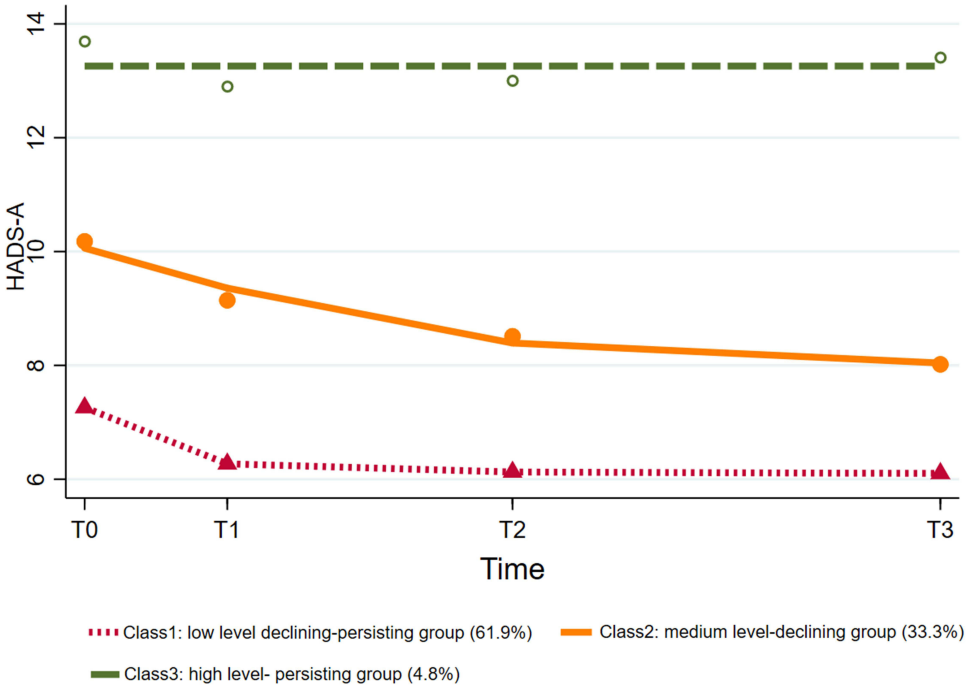

Figure 4 Trajectories of anxiety in COPD patients.

The GBDTM Analysis of Inhaled Medication Adherence and Anxiety

Most of the patients with the three anxiety trajectories belonged to the high adherence-persisting group, indicating that there was no significant correlation between the trajectories of inhaled medication adherence and those of anxiety. Details are shown in Table 5.

Discussion

Dynamic Changes in Inhaled Medication Adherence of Patients with COPD

Overall, nearly one-third of patients with COPD had poor inhaled medication adherence during the follow-up period, and the number and proportion of patients with poor adherence tended to decrease initially and then increase over time.

The number and proportion of patients with poor adherence reached its nadir in T1, which could be attributed to the fact that (i) the patients' physical condition was still unstable shortly after discharge from the hospital, and they might adhere to the use of inhaled medication due to the fear of re-exacerbation and the urgency to relieve their symptoms, (ii) the patients received medication guidance and health education on the disease from healthcare professionals (HCPs) during their hospitalization, and levels of support from caregivers was also higher in their hospitalization periods and shortly after discharge, thus, the patients were more likely to adhere to inhaled medication.[42–44]

Table 5 Conditional Probability of Inhaled Medication Adherence Trajectories Based on Anxiety Trajectories (%)

Trajectories of Inhaled Medication Adherence	Trajectories of Anxiety		
	Low Level Declining-Persisting Group	Medium Level-Continuously Declining Group	High Level-Persisting Group
Low adherence rising-declining group	13.3	18.8	40.0
Low adherence rising-persisting group	11.7	17.4	10.0
Medium-low adherence-persisting group	17.2	21.7	0
High adherence-persisting group	57.8	42.0	50.0

From T2 to T3, the number and proportion of patients with poor adherence gradually increased, perhaps due to the medication adherence of patients with COPD has a "symptomatic effect". With the prolongation of the post-hospital discharge period, patients' conditions gradually stabilize, resulting in slackness and neglect of the importance of medication adherence, and patients may start or discontinue inhaled medication arbitrarily according to their subjective feelings.[44,45]

The inhalation medication adherence of patients with COPD is dynamic, which reminds HCPs that it is necessary to shift the perspective of adherence assessment and track inhaled medication use in patients with COPD after discharge, especially one month after discharge.

The Trajectories of Change in Inhaled Medication Adherence of Patients with COPD

In this study, the trajectory of inhaled medication adherence in patients with COPD was classified into four categories: a high adherence-persisting group (50.4%), a medium-low adherence-persisting group (18.4%), a low adherence rising-persisting group (15.0%), and a low adherence rising-declining group (16.3%). Chen et al[18] noted that medication adherence trajectories among patients with chronic diseases were synthesized into six categories: adherence, non-adherence, decreasing adherence, increasing adherence, fluctuating adherence and moderate adherence, which encompassed nearly all trajectory trends, resulting in similar trajectory naming in this study compared to Chen et al's findings. However, we identified a trajectory—Low adherence rising-persisting group—that was not adequately described in previous reviews. This group exhibited a pattern of sustained improvement in adherence from T0 to T1, followed by maintenance at the adherence level.

The highest percentage of patients was in the group with persistently high adherence, which is similar to the results of other studies of medication adherence trajectories in patients with chronic diseases.[46–48] The reason for this may be that more than 2/3 of the patients in this study had a disease duration of ≥5 years; they had some knowledge about the disease and medication, and their years of experience with the disease made them gradually develop the habit of taking medication on time. Second, 76.3% of the patients in this study were GOLD 3 or GOLD 4, which made them dependent on medication.[49] However, the patients included in this study all originated from the same tertiary hospital, and their inhaled medication adherence may be related to the well-established medical resources and higher levels of health education in this hospital. Furthermore, the data collection based on the questionnaire may have potential recall or social desirability bias. These factors limit the generalizability of the research result to a certain extent.

The proportion of patients with persistently poor adherence (34.7%) in this study was higher than that in the above mentioned studies,[46–48] perhaps because compared to oral medication for diabetes, hypertension, etc, the medication for patients with COPD is more complex, and inhalation devices have a certain degree of finesse and are more difficult to operate.[50] In addition, the inhaled devices are more expensive, and the family's financial burden caused by long-term medication use may also directly affect the patient's adherence to medication.

Factors Associated with the Heterogeneity of the Inhaled Medication Adherence Trajectory of Patients with COPD

Duration of Inhalation Device Use

According to the results of this study, patients with COPD with less than a year of inhalation device use were less likely to be categorized into C1 and C3 than into C4. Compared with C2, patients with ≤2 years of inhalation device use were less likely to be categorized into C1 and C3. Several studies[51–53] have demonstrated that the duration of inhalation device use in patients with COPD was positively correlated with their inhaled medication adherence, probably because patients with a short duration of inhalation device use do not have sufficient knowledge about inhalation devices and their importance, and they are more prone to inhalation technique errors. Effective drug delivery depends on the correctness of the patient's inhalation technique, and when the patients make inhalation errors, the efficacy of the drug decreases and the adverse drug reactions more commonly occur, leading to adverse clinical outcomes and increased healthcare burden.[54] When the patient cannot benefit from the use of the inhalation device, the device is used less frequently.[55] The longer the duration of inhalation device use, the greater the opportunity for patients to receive medication-related instruction, and

the more familiar they become with inhalation device procedures, precautions, and drug effects, which might be conducive to a reduction in the frequency of inhalation technique errors and an increase in adherence. HCPs could focus on COPD patients with short duration of inhalation devices use, demonstrating the steps involved in appropriately using these devices to them during their hospitalization periods and assess them on the spot so that they can correct their errors promptly, and consider carrying out regular follow-up assessments of their inhalation status after discharge, reinforcing the correct inhalation technique.

Health Literacy

Using C4 as a reference, patients with high health literacy were more likely to be in C1, C2, and C3. Muellers et al[56] reported that low health literacy was significantly associated with low medication adherence in patients with COPD, and this effect was not mitigated by the presence of a caregiver. The reason may be that patients with low health literacy have insufficient ability to acquire, understand, and apply COPD-related knowledge, which leads to inadequate understanding of their own conditions and treatment options, and they are prone to doubt treatment options and more likely to adopt unscientific behaviors to deal with doubts and difficulties in the course of treatment.[57] Conversely, patients with high health literacy actively seek treatment-related information to enhance disease management and demonstrate greater engagement during medical consultations, accurately understanding and adhering to prescribed medications.[57] In addition, the Knowledge-Attitude-Practice Model[58] states that knowledge is the foundation, attitude is the driving force, and possessing certain kinds of knowledge is a prerequisite for individuals to exert their subjective initiative and take action. In short, the more patients understand COPD and related medications, the better they grasp the beneficial impact of inhaled medications on disease control. This leads to greater confidence in adhering to inhaled medication regimens, which is closely linked to improved medication adherence. For COPD patients with low health literacy, HCPs could actively offer diverse and personalized health education while arranging regular and continuous follow-up visits for the patients after their discharge to strengthen their memory of COPD-related knowledge.

Beliefs About Medicines

With reference to C4, patients with higher levels of beliefs about medicines were more likely to be categorized into C1, C2, and C3. Compared to C2, patients with higher levels of beliefs about medicines were more likely to be in C1. Liu et al[43] found that beliefs about medicines had direct effects on inhaled medication adherence by using path analysis. Beliefs about medicines include necessary beliefs and concern beliefs, with necessary beliefs representing patients' perceptions and attitudes about the necessity of medication and concern beliefs representing patients' concerns and fears about medication. If patients' necessary beliefs outweigh their concern beliefs—expecting that taking medication will control the disease and improve symptoms, they will be more inclined to adopt correct medication management strategies.[59] Meanwhile, the Health Belief Model[60] suggests that patients' health behaviors are the result of a cost-benefit analysis, which is dependent on six key elements: (i) perceived susceptibility, (ii) perceived severity, (iii) perceived benefits, (iv) perceived barriers, (v) self-efficacy, and (vi) cues for action. Patients are more likely to adopt healthy behaviors when they are aware of the consequences of poor ones and recognize the benefits of healthy ones through their perceptions of disease susceptibility and severity, and when they believe they can successfully change their behavior. For patients with poor medication beliefs, HCPs could unequivocally inform them of the necessity and importance of long-term medication adherence, pay attention to their experience of inhaled medication use, and identify and address negative feedback promptly.

The GBDTM analysis in this study demonstrated that there was a positive relationship between the trajectories of inhaled medication and trajectories of beliefs about medicines in patients with COPD. During inhaled medication use, patients continuously weigh the benefits and drawbacks of adherence, such as medication efficacy, adverse effects, and costs, while their perception of disease severity evolves with clinical progression. All of these factors combine to drive changes in beliefs about medicines, which in turn affect medication adherence.[61,62] Moreover, positive beliefs about medicines promote medication adherence, and good medication adherence also strengthens a patient's belief in medicines. When patients experience improvement or symptom relief through regular medication use, their confidence in medication will be further enhanced, which strengthens their beliefs about medicines, and this positive feedback

mechanism can motivate them to follow the treatment regimen more actively.[63] Therefore, HCPs could consider paying attention to the dual monitoring of inhaled medication adherence and beliefs about medicines among patients with COPD, identifying patients with persistently low or declining beliefs about medicines as early as possible, and adopting personalized interventions according to the trend of their beliefs about medicines, to form a benign cycle of "belief enhancement-adherence enhancement-symptom improvement."

Anxiety

Patients with low levels of anxiety were more likely to be in C1 compared to C2. Yu et al[64] found that anxiety was a risk factor for non-adherence to inhaled medication. However, this study also showed that patients in C2 had more severe anxiety than those in C4, which may be related to higher levels of social support for those in C2. Anxious individuals are more sensitive to potential threats, prompting them to choose avoidance behavior as an adaptive response to alleviate anxiety and fear; in addition, anxious individuals may exaggerate the cost and likelihood of threats, leading to overly pessimistic expectations.[65] COPD patients with high levels of anxiety may exhibit a negative attitude toward treatment due to doubts and concerns about drug efficacy and adverse reactions, as well as uncertainty and fear of disease progression, leading to increased medication adherence hesitancy. HCPs could consider paying attention to the anxiety of patients with COPD, strengthening communication with them, and establishing a harmonious relationship with them.

The GBDTM analysis in this study showed that there was no significant correlation between inhaled medication adherence trajectories and anxiety trajectories. A systematic review by Volpato et al[66] suggested that anxiety might have an indirect impact on patient adherence, and anxiety in COPD patients might affect their adherence by reducing treatment confidence and self-efficacy or increasing cognitive impairment. However, due to Class 3 comprising slightly less than 5% of the sample, the analysis within this subgroup may be underpowered, and the stability of these findings warrants validation in future studies with larger samples.

Perceived Social Support

Compared with those in C4, patients in C2 had higher levels of perceived social support. Social support refers to the resources and assistance that individuals perceive or receive in terms of tools, emotions, and information,[67] which is an external factor contributing to the formation of healthy behaviors in patients with chronic diseases and is positively correlated with medication adherence.[68] Patients with high levels of social support can receive more care, supervision, or financial support from family and peers, which may reduce the psychological burden caused by the disease, giving them stronger confidence in facing various difficulties and obstacles, having a positive impact on treatment adherence.[69] Therefore, the construction of a multifaceted social support system may contribute to improved inhaled medication adherence in patients with COPD. In terms of medical support, HCPs might consider paying attention to the difficulties and obstacles they face during inhaled medication use and providing them with comprehensive professional support to help improve their medication experience. Regarding family support, family members could be encouraged to proactively participate in the patients' medication management and actively remind and monitor their medication. In terms of peer support, patients with COPD might consider joining wardmate support groups to facilitate the formation of peer support networks through exchanging disease management and medication experiences.

Strengths and Limitations

Strengths

This study employed a longitudinal design to systematically track the developmental trajectories of inhaled medication adherence among COPD patients. Unlike cross-sectional studies that only capture adherence at a single time point, the longitudinal approach reveals the dynamic fluctuations of adherence over time, providing a more comprehensive understanding of its evolution. Furthermore, GBTM was applied to identify heterogeneous patterns of inhaled medication adherence, highlighting significant differences in medication behavior changes across patient subgroups, which provides insight into the complexity and diversity inherent in the medication behavior of COPD patients and a basis for developing phased and personalized intervention strategies, thereby contributing to the field of inhaled medication adherence in COPD.

Building on logistic regression, this study further employed GBDTM to explore how the trajectories of beliefs about medicines and anxiety influence the developmental trajectories of inhaled medication adherence in patients with COPD. This approach captures the longitudinal interplay between psychological factors and adherence behaviors, which transcends the limitations of traditional regression that only addresses static correlations. By identifying the joint developmental patterns of adherence and psychological trajectories, this study provides new empirical evidence for understanding the dynamic mechanisms underlying medication adherence in COPD patients.

Limitations

First, the study only included patients with COPD who have been using inhalation devices for more than three months, recruited via convenience sampling from one tertiary-level hospital, and the sample of this study consisted predominantly of male patients, which may limit broader applicability to other settings, particularly primary care or more gender-balanced COPD populations. Secondly, the follow-up period of this study was only six months, and this was insufficient to fully reflect the long-term changes in inhaled medication adherence. Thirdly, this study employed questionnaire surveys with telephone follow-up, which may have potential recall or social desirability bias, leading to potential overestimation or underestimation of measures. Fourth, the sensitivity analysis was not conducted to assess the impact of loss to follow-up on model fit, which to some extent limits a comprehensive evaluation of the robustness of our findings.

Future studies could (i) focus on patients with COPD who are using inhalation devices for the first time to promote intervention by early screening of patients with poor adherence, (ii) consider conducting multi-center surveys with larger sample sizes and expanding the follow-up period to validate this study's results, (iii) apply electronic monitoring devices to achieve an objective long-term assessment of inhaled medication adherence, (iv) examine the predictive value of heterogeneous trajectories for key clinical outcomes, such as acute exacerbation, hospitalization, or quality of life.

Conclusions

In summary, this study reveals that inhaled medication adherence in patients with COPD is dynamic, and its developmental trajectories exhibit heterogeneity associated with multidimensional factors. The identification of heterogeneous trajectories of inhaled medication adherence provides a basis for screening potential intervention candidates among COPD patients, facilitating early and targeted interventions for this population. Based on our findings, HCPs may consider focusing on changes in medication use behaviors of COPD patients after discharge, particularly adherence fluctuations within the first month. Additionally, it is advisable to prioritize dynamic adherence assessments for COPD patients with ≤2 years of inhaler device use, low levels of health literacy, low levels of belief in medicines, high levels of anxiety, and low levels of social support. Future research should explore the associations between specific trajectory groups and clinical outcomes to enhance the translational value of these findings. Several methodological limitations should be acknowledged, including the use of single-center convenience sampling, data collection through self-reported questionnaires, and the absence of sensitivity analyses for the trajectory models, which may limit the generalizability of the findings to some extent.

Abbreviations

COPD, Chronic Obstructive Pulmonary Disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; WHO, World Health Organization; ICS, Inhaled Corticosteroid; LABA, Long-acting Beta 2 Receptor Agonists; LAMA, Long-acting Antagonist; pMDI, Pressurized Metered Dose Inhaler; DPI, Dry Powder Inhaler; SMI, Soft Mist Inhaler; TAI, Test of The Adherence to Inhalers; CAT, COPD Assessment Test; GBTM, Group-Based Trajectory Modeling; GBDTM, Group-Based Dual Trajectory Model; BIC, Bayesian Information Criteria; aCCI, age-adjusted Charlson Comorbidity Index; COPD-Q, Chronic Obstructive Pulmonary Disease Knowledge Questionnaire; BMQ-Specific, Beliefs about Medicines Questionnaire-Specific; HADS, Hospital Anxiety and Depression Scale; PSSS, Perceived Social Support Scale; AIC, Akaike Information Criterion; AvePP, Average Posterior Probability; TOL, Tolerance; VIF, Variance Inflation Factor.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author (Ronghua Li) on reasonable request.

Ethics Approval and Informed Consent

The research was approved by the Ethics Committee of Guangzhou Medical University (Grant number: 202403019), and written informed consents were obtained from all participants. The study protocol followed the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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