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Suboptimal peak inspiratory flow rate: a noticeable risk factor for inhaler concordance in patients with chronic airway diseases

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ABSTRACT

Background Inhaler concordance and the peak inspiratory flow rate (PIFR) are important determinants of treatment effects in patients with chronic airway diseases. Adequate PIFR is required for driving aerosol medication into the lower respiratory tract. However, the relationship between them has not been discussed previously. This study aimed to describe the characteristics of inhaler concordance and PIFR in Chinese patients with chronic airway diseases and discuss the associated variables and the relationship between them.

Methods In this single-centre, observational study, a total of 680 patients with chronic airway diseases were enrolled from July 2021 to April 2023. We collected data on the socio-demographic and clinical variables of inhaler concordance using the test of adherence to inhalers (TAI) and PIFR. Multivariate logistic regression was conducted to examine variables related to inhaler concordance and PIFR.

Results A total of 49.4% of patients had low concordance. Patients with chronic obstructive pulmonary disease (COPD) were more concordant than patients with asthma (mean TAI score: 43.60 vs 41.20; p<0.01), while there was no difference in concordance between the asthma-COPD overlap group and the asthma or COPD group. Suboptimal PIFR (adjusted OR, 1.61; 95% CI 1.04 to 2.51) increased the risk of poor concordance among all patients, while triple therapy (adjusted OR, 0.60; 95% CI 0.35 to 0.86) reduced the risk. A total of 54.9% of patients had suboptimal PIFR. Older age, lower educational level, use of dry powder inhalers and lower forced expiratory volume in 1 s % predicted were significantly correlated with insufficient PIFR. Subgroup analysis revealed a greater proportion of patients with insufficient PIFR during exacerbation than during the stable phase (61.7% vs 43.5%, p<0.001).

Conclusion Inhaler concordance was low, and suboptimal PIFR was a risk factor for poor concordance among Chinese patients with chronic airway diseases. In addition, current inhalation devices may not be suitable, and PIFR reassessment should be considered for patients with COPD during exacerbation.

Trial registration number The study was registered in chictr.org.cn (ChiCTR2100052527) on 31 October 2021.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Inhaler concordance and the peak inspiratory flow rate (PIFR) are important determinants of treatment effects in patients with chronic airway diseases. Adequate PIFR is required for driving aerosol medication into the lower respiratory tract. However, the relationship between them has not been discussed previously.

WHAT THIS STUDY ADDS

⇒ Inhaler concordance was low, and suboptimal PIFR was a risk factor for poor concordance among Chinese patients with chronic airway diseases.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study not only provides a new perspective for clinicians when improving patients' inhaler concordance, but also provides a reminder that clinicians should pay attention to the PIFR re-evaluation and re-selection of the inhalation device for patients with chronic obstructive pulmonary disease during exacerbation.

INTRODUCTION

Chronic respiratory diseases, especially chronic obstructive pulmonary disease (COPD) and asthma, result in substantial economic and social burdens on healthcare systems worldwide, with annually increasing morbidity and mortality.[1] The China Pulmonary Health study showed that the prevalence of COPD in China was 13.7% among patients older than 40 years,[2] and the prevalence of asthma was 4.2% among patients older than 20 years.[3] Thus, optimising the management and achieving effective control of chronic airway diseases is essential but continues to be a challenge.

It is widely known that inhalers are the pillar of treatment for chronic airway diseases, the effectiveness of which heavily depends on inhaler concordance.[4] Nonetheless, some

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epidemiological studies have indicated that poor concordance is still prevalent, which poses a major impediment to achieving optimal outcomes.[4–6] For example, Alexopoulos *et al*[7] reported that poor concordance led to 11.5% more exacerbations and 14.1% more hospitalisations related to COPD per year. A large Italian cohort study demonstrated that regular use of inhaled drugs led to higher survival rates among moderate-severe patients with COPD.[8] Therefore, evaluating inhaler concordance among patients with chronic airway diseases is imperative. The test of adherence to inhalers (TAI) is a well-accepted and professional instrument for assessing patients' inhaler concordance in chronic airway diseases.[9] Despite its good applicability in European and American populations,[10–12] the TAI has not yet been widely used in China.

Medication concordance varies tremendously depending on demographic factors, disease-related factors, medication-related factors, etc.[13 14] Inhalers are typically classified into three types: dry powder inhalers (DPIs), pressurised metred-dose inhalers (pMDIs) and Respimat soft mist inhalers (SMIs). The efficacy of inhalers primarily relies on the peak inspiratory flow rate (PIFR) generated by patients to overcome the inhalation device's internal resistance during a forced inspiratory manoeuvre.[15 16] Breath-actuated DPIs require patients to generate sufficient PIFR to disaggregate and disperse the drug formulation into respirable particles. Conversely, effective drug delivery for pMDIs, which requires slow and deep inhalation, depends on a lower PIFR.[17] The optimal range of the PIFR is generally considered 60–90 L/min for DPIs and 20–60 L/min for pMDIs.[15 18–21] If a patient's PIFR does not match the prescribed inhaler, inadequate distal airway drug deposition may occur, thereby resulting in detrimental clinical consequences.[22] A few studies have recently revealed that suboptimal PIFR may increase the risk of all-cause and COPD-related hospital readmissions among patients with COPD.[23]

Although some European, North and South American studies have assessed inhaler concordance and PIFR in patients with COPD or asthma, little is known about patients with asthma-COPD overlap (ACO). In this study, we aimed to describe the characteristics of inhaler concordance and PIFR in Chinese patients with chronic airway diseases and discuss the potential risk factors for poor concordance, especially whether PIFR affects inhaler concordance.

METHODS

Study design, setting and participants

A single-centre observational study was performed at a 3500-bed tertiary teaching hospital, Second Xiangya Hospital of Central South University, Changsha, China. A total of 680 patients were consecutively enrolled from 1 July 2021 to 1 April 2023. The eligibility criteria included the following: (1) over 18 years of age; (2) confirmed diagnosis of COPD, asthma or ACO according to the guidelines[24–26]; and (3) treatment with usual inhalers for at least the previous 3 months. The exclusion criteria were as follows: (1) inability to complete the questionnaire due to severe physical or mental illness; and (2) concomitant bronchiectasis, pulmonary embolism, interstitial lung disease or other respiratory diseases.

We collected data on baseline characteristics, including age, sex, body mass index (BMI), educational level, smoking history, acute exacerbations in the previous year, years since diagnosis, medication duration, modified Medical Research Council (mMRC) dyspnoea grade and COPD Assessment Test (CAT) score (assessed at stability or during exacerbation) for patients with COPD/patients with ACO, asthma control test (ACT) score (assessed at stability or during exacerbation) for patients with asthma/patients with ACO, inhalers, inhalation devices and pulmonary function.

Exacerbations are defined as an acute worsening of respiratory symptoms that result in additional therapy. These events are classified as mild (treated with short-acting bronchodilators (SABDs) only), moderate (treated with SABDs plus antibiotics and/or oral corticosteroids) or severe (patient requires hospitalisation or visits the emergency room).[25]

Evaluation instruments

Concordance was assessed by the 12-item TAI consisting of 10 items for patients and 2 additional items for clinicians.[9 27] The scoring range for each of the 10 items varied from 1 (worst concordance) to 5 (best concordance), with a total sum score between 10 and 50 indicating good (50), intermediate (46–49), or poor (≤45) concordance. The final two items were scored as 1 or 2 for poor or good knowledge of the regimen and/or inhalation technique, respectively, with a range from 2 to 4. In addition to the concordance level, this scale also described the non-concordance pattern as follows: erratic, deliberate or unwitting.

The PIFR was assessed using an In-Check Dial (Clement Clark International, Harlow, UK) device capable of measuring inspiratory flow rates in the range of 15–120 L/min (±10 L/min).[19] In-Check Dial contains five resistance groups for DPIs classified as low (R1), medium-low (R2), medium (R3), medium-high (R4) and high (R5), whereas no resistance (R0) is set for pMDIs or SMIs. In this study, PIFR was assessed in two different ways: (1) $PIFR_s$ against five degrees of resistance (R1–R5), which requires fast and forceful inhalation, and (2) $PIFR_0$ against a resistance of zero (R0), which requires slow and gentle inhalation. Participants were then stratified into three groups: patients with optimal PIFR (60–90 L/min for DPIs or 20–60 L/min for pMDIs/SMIs), patients with excessive PIFR (>90 L/min for DPIs or >60 L/min for pMDIs/SMIs) and patients with insufficient PIFR (<60 L/min for DPIs or <20 L/min for pMDIs/SMIs) based on PIFR measurements against the resistance of the patient's current inhaler. Suboptimal PIFR is defined as excessive or insufficient PIFR. Notably, PIFR was considered

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optimal for patients using multiple inhalers only when their inhalation capacity fell within the ranges for all inhalers.[28]

Researchers orally taught patients about inhaler techniques and correct breathing manoeuvres. The PIFR was measured under the guidance of researchers.[15] For patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD), the PIFR was measured within 1–3 days of the onset of exacerbation and once again at a stable status.[29] The PIFR at each resistance was measured consecutively three times, and the maximum was recorded.

Statistical analysis

Descriptive statistical analysis of socio-demographic and clinical characteristics was performed, and categorical variables are presented as counts (n) with percentages (%) and continuous variables are presented as the means with SDs when normally distributed or as the medians with IQRs otherwise. Qualitative variables were compared using a χ^2 test or Fisher's exact test, while quantitative variables were analysed using Student's t-test, analysis of variance, or the Mann-Whitney U test.

Covariates included age, sex, BMI, educational level, smoking status, disease diagnosis, ACT score or CAT score, medication, inhalation device and PIFR. Bivariate analyses were conducted to select covariates with p<0.05, and then we included these significant covariates in the multivariate regression to determine risk factors associated with poor concordance and insufficient PIFR. Data analyses were performed using IBM SPSS Statistics V.25.0. P values were two-tailed, and statistical significance was set at 0.05.

RESULTS

Characteristics of the sample

Among 680 patients (mean (SD) age 62.54 (11.43) years, 80.7% men, mean (SD) BMI 22.26 (3.43) kg/m^2), 452 (66.5%) were diagnosed with COPD, 151 (22.2%) with asthma and 77 (11.3%) with ACO (online supplemental figure S1). The median (IQR) exacerbation in the past year was 1.00 (0.00–2.00) for all patients, and the median (IQR) forced expiratory volume in 1 s % (FEV_1%) predicted was 49.05 (32.52–72.50). Compared with patients with COPD and patients with ACO, patients with asthma had a significantly greater percentage of women, a greater percentage of younger individuals, a lower proportion of smokers, fewer exacerbations in the past year and better lung function (table 1). Despite the similarities in most baseline characteristics between the two groups, patients with ACO were younger than patients with COPD.

Medication concordance for chronic airway diseases

Overall, 49.4% of patients presented poor concordance to inhalers. Patients with COPD were more concordant than patients with asthma (mean TAI-10 score: 43.60 vs 41.20; p<0.01, table 2). The concordance level was not significantly different between the ACO group and the COPD (43.29 vs 43.60, p=0.148, table 2) or asthma (43.29 vs 41.20, p=0.518, table 2) group. In addition, the pattern of non-concordance was more frequently erratic and deliberate in patients with asthma than in patients with COPD and patients with ACO (p<0.001), whereas there was no significant difference in the unwitting behaviour among the three groups.

Measured peak inspiratory flow rate

Finally, 532 participants completed the PIFR tests (online supplemental figure S1). The PIFR values among patients with COPD were lower than those among patients with asthma and patients with ACO regardless of resistance (table 3). A significantly greater proportion of patients with COPD had insufficient PIFR than did patients with asthma (38.5% vs 22.1%, p<0.01, table 3) and patients with ACO (38.5% vs 22.2%, p<0.01, table 3).

The results showed that PIFR was prone to be insufficient in Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages 3 and 4 versus GOLD stages 1 and 2 (51.6% vs 29.9%, p<0.05, online supplemental figure S2A) and in groups C and D versus groups A and B (51.5% vs 35.1%, p<0.05, online supplemental figure S2A) among patients with COPD. Moreover, patients with COPD had a greater percentage of optimal PIFR in groups A and B than in groups C and D (50.0% vs 36.8%, p<0.05, online supplemental figure S2A). In addition, we observed significantly lower PIFRs at any resistance and a greater percentage of insufficient PIFR among patients with COPD during acute exacerbation than among patients with COPD during the stable phase (61.7% vs 43.5%, p<0.001, online supplemental figure S2B and table S1 and table S1). However, there were no significant differences in the subgroup analyses of patients with asthma (online supplemental figure S2C). Subgroup analyses of patients with ACO revealed that the patients with GOLD stages 3 and 4 versus GOLD stages 1 and 2 had a greater proportion of insufficient PIFR (43.8% vs 0.0%, p<0.05, online supplemental figure S2D).

Risk factors for poor concordance

Table 4 shows the results of a logistic regression analysis of factors that were independently associated with poor concordance among all studied patients and three disease subgroups. Univariable factors, such as lower educational level, short treatment time, mono-/dual combination therapy, the use of multiple inhalation devices at one time and suboptimal PIFR, were found to be significantly related to poor concordance among patients with COPD. As indicated by the analysis of the total sample, multivariate analysis revealed that patients with COPD with suboptimal PIFR were more at risk of poor concordance than those with optimal PIFR (adjusted OR, 1.93; 95% CI 1.12 to 3.31, table 4). Rather than mono-/dual combination therapy, patients receiving triple therapy had

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Table 1 Baseline characteristics of the study population and disease subgroups

Variables	Total (n=680)	COPD group (n=452)	Asthma group (n=151)	ACO group (n=77)	P value
Age (years)*	62.54±11.43	66.61±7.94	51.01±13.66†	61.25±7.85*‡	<0.001
Sex, male	549 (80.7)	423 (93.6)	58 (38.4)†	68 (88.3)‡	<0.001
Body mass index (kg/m^2)*	22.26±3.43	21.84±3.29	23.42±3.39†	22.46±3.83	<0.05
Educational level					<0.001
Primary	220 (32.4)	172 (38.1)	24 (15.9)†	24 (31.2)‡	–
Secondary	232 (34.1)	146 (32.3)	60 (39.7)	26 (33.8)	–
High school	121 (17.8)	78 (17.3)	23 (15.2)	20 (26.0)	–
University and above	107 (15.7)	56 (12.3)	44 (29.2)†	7 (9.0)‡	–
Smoking index (pack-years)	35.00 (0.00–50.00)	40.00 (30.00–60.00)	0.00 (0.00–0.00)†	30.00 (10.00–49.00)*‡	<0.05
Smoking status					<0.001
Current smoker	145 (21.4)	110 (24.3)	13 (8.6)†	22 (28.6)‡	–
Ex-smoker	358 (52.6)	295 (65.3)	22 (14.6)†	41 (53.2)‡	–
Never smoker	177 (26.0)	47 (10.4)	116 (76.8)†	14 (18.2)‡	–
Years since diagnosis	4.00 (2.00–7.00)	4.00 (2.00–7.00)	4.50 (1.00–10.00)	4.50 (3.00–7.00)	0.570
Exacerbations in the previous year	1.00 (0.00–2.00)	1.00 (0.00–3.00)	1.00 (0.00–1.00)†	1.00 (0.00–3.00)‡	<0.001
Medication time (years)	2.35 (1.00–5.00)	3.00 (1.00–5.00)	1.30 (0.41–3.00)	3.00 (1.00–5.00)	<0.001
CAT score*	–	18.90±6.21	–	17.94±5.92	0.204
mMRC dyspnoea grade	–	2.00 (2.00–3.00)	–	2.00 (1.00–3.00)	0.119
ACT score	–	–	20.00 (18.00–22.00)	19.00 (16.00–21.00)	<0.01
Medication					<0.001
LAMA	66 (9.7)	59 (13.0)	3 (2.0)†	4 (5.2)	–
ICS+LABA	301 (44.3)	137 (30.3)	135 (89.4)†	29 (37.7)‡	–
LABA+LAMA	92 (13.5)	88 (19.5)	0 (0.0)†	4 (5.2)*‡	–
ICS+LABA+LAMA	221 (32.5)	168 (37.2)	13 (8.6)†	40 (51.9)‡	–
Inhalation device					<0.001
DPIs	479 (70.4)	305 (67.5)	135 (89.4)†	39 (50.6)*‡	–
pMDIs/SMIs	86 (12.7)	64 (14.2)	7 (4.6)†	15 (19.5)‡	–
DPI+DPI/SMI	115 (16.9)	83 (18.3)	9 (6.0)†	23 (29.9)‡	–
Lung function					–
Post-BD FEV_1% predicted	49.05 (32.52–72.50)	39.50 (28.00–55.60)	88.45 (73.17–100.92)†	50.85 (33.87–65.15)*‡	<0.001
Post-BD FEV_1/FVC (%)	44.32 (33.82–60.14)	38.62 (31.24–49.07)	74.17 (64.46–79.56)†	44.00 (34.29–54.33)‡	<0.001

Continued

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Table 1 Continued

Variables	Total (n=680)	COPD group (n=452)	Asthma group (n=151)	ACO group (n=77)	P value

Data are presented as n (%) or medians (IQRs) unless otherwise stated.
*Data are presented as mean±SD.
†Compared with the COPD group.
‡Compared with the asthma group.
ACO, asthma-COPD overlap; ACT, asthma control test; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; DPIs, dry powder inhalers; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting beta-adrenoceptor agonist; LAMA, long-acting muscarinic receptor antagonist; mMRC, modified Medical Research Council; pMDIs, pressurised metred-dose inhalers; Post-BD, postbronchodilator; SMIs, Respimat soft mist inhalers.

significantly lower odds of poor concordance (adjusted OR, 0.47; 95% CI 0.27 to 0.80, table 4). Notably, patients with asthma with lower ACT scores were prone to be less concordant (adjusted OR, 0.82; 95% CI 0.70 to 0.95, table 4), and patients with ACO with higher CAT scores were more likely to have poor concordance (adjusted OR, 1.13; 95% CI 1.01 to 1.26, table 4).

Risk factors for insufficient PIFR

Univariate analysis revealed significant differences in age, BMI, educational level, smoking status, history of severe exacerbations in the previous year, asthma, inhalation devices, number of inhalers, exacerbation or stable status and FEV_1% predicted between the insufficient and sufficient groups in the total population. Multivariate analysis demonstrated that a higher educational level and the use of pMDIs/SMIs were protective factors (adjusted OR, 0.54; 95% CI 0.28 to 1.01 and adjusted OR, 0.15; 95% CI 0.04 to 0.55, respectively, table 5), whereas older age was a risk factor for insufficient PIFR (adjusted OR, 1.05; 95% CI 1.01 to 1.08, table 5). Subjects with a lower FEV_1% predicted had an increased risk of insufficient PIFR (adjusted OR, 0.97; 95% CI 0.96 to 0.99, table 5).

For patients with COPD, the results indicated that lower educational levels, use of DPIs, a history of severe exacerbations in the previous year and a lower FEV_1% predicted increased risk of insufficient PIFR (table 5). Further subgroup analyses revealed that the use of DPIs, groups C and D (adjusted OR, 3.89; 95% CI 1.05 to 14.46, online supplemental table S2) and a lower FEV_1% predicted were independent predictors of insufficient PIFR in patients with COPD during exacerbation. Insufficient PIFR in patients with asthma was associated with older age (adjusted OR, 1.10; 95% CI 1.01 to 1.20, table 5) and a longer course of disease (adjusted OR, 1.12; 95% CI 1.02 to 1.24, table 5). A lower FEV_1% predicted was the only risk factor for insufficient PIFR in patients with ACO (adjusted OR, 0.85; 95% CI 0.72 to 1.00, table 5).

DISCUSSION

This study described the characteristics of inhaler concordance and PIFR in Chinese patients with chronic airway diseases. Furthermore, this study demonstrated that suboptimal PIFR was an important determinant of poor inhaler concordance among patients with chronic airway diseases. Therefore, not only lung function but also inhaler concordance and PIFR should be assessed during the management of chronic airway diseases.

In accordance with Spanish studies,[30] our study revealed that Chinese patients with COPD did not show an optimal proportion of good inhaler concordance, and Chinese patients with asthma were even non-concordant. Our results showed that patients with COPD were older and had worse lung function than patients with asthma, which might make patients with COPD more symptomatic and more likely to experience frequent exacerbations, thus leading them to perceive the necessity of inhalers

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Table 2 Concordance level, TAI score and non-concordance behaviour patterns in overall patient and disease subgroups

Variable	Total (n=680)	COPD group (n=452)	Asthma group (n=151)	ACO group (n=77)	P value
Concordance level					<0.001
Good-intermediate concordance	344 (50.6)	250 (55.3)	54 (35.8)*	40 (51.9)	
Poor concordance	336 (49.4)	202 (44.7)	97 (64.2)*	37 (48.1)	
Total score	43.03±7.36	43.60±7.47	41.20±6.97*	43.29±7.00	<0.01
Erratic	21.25±4.31	21.60±4.30	20.11±4.10*	21.38±4.43	<0.01
Deliberate	21.79±3.79	22.00±3.78	21.09±3.75*	21.91±3.83	<0.05
Unwitting	3.42±0.65	3.45±0.64	3.32±0.65	3.42±0.65	0.167
Non-concordance behaviour†					<0.001
Sporadic	455 (66.9)	281 (62.2)	124 (82.1)*	50 (64.9)‡	
Deliberate	405 (59.6)	258 (57.1)	106 (70.2)*	41 (53.2)‡	
Unwitting	335 (49.3)	210 (46.4)	87 (57.8)	38 (49.1)	

Data are presented as the mean±SD or numbers (%).
*Compared with the COPD group.
†More than one behaviour may be present in the same case.
‡Compared with the asthma group.
ACO, asthma-COPD overlap; COPD, chronic obstructive pulmonary disease; TAI, test of adherence to inhalers.

and adhere to treatment.[31] Some similar characteristics may explain why the concordance level between the ACO group and the COPD group was not significantly different. Given these results, we recommend assessing inhaler concordance and strengthening disease education for Chinese patients with chronic airway diseases to avoid worsening outcomes induced by treatment interruption.

Although some studies have described the characteristics of inhaler concordance and PIFR,[29–32] the association between them has not been discussed in previous studies. Our study revealed that a suboptimal PIFR is a significant determinant of poor concordance among Chinese patients with chronic airway diseases, especially patients with COPD. To obtain the optimal efficacy of inhalers, inhalation must be able to generate an optimal PIFR to guarantee adequate penetration of the medication into the airways.[28] Conversely, patients might lose confidence and eventually give up long-term inhaled therapy due to suboptimal PIFR, resulting in a compromised treatment effect. In addition, patients with COPD receiving triple therapy had a decreased risk of poor concordance. Many studies have confirmed the potential advantages of single-inhaler triple therapy (SITT) in improving

Table 3 Distribution and level of PIFR among study patients

Variable	Total (n=532)	COPD group (n=374)	Asthma group (n=95)	ACO group (n=63)	P value
Resistance class					
R0	120.00 (90.00–120.00)	119.00 (85.00–120.00)	120.00 (111.50–120.00)*	120.00 (110.00–120.00)*	<0.001
R1	82.00 (66.00–100.00)	77.50 (62.00–92.00)	100.50 (81.75–115.25)*	90.00 (80.50–106.00)*	<0.001
R2	74.00 (60.00–88.25)	68.00 (56.00–81.25)	87.50 (70.75–100.00)*	80.00 (70.00–95.25)*	<0.001
R3	65.00 (53.00–80.00)	60.00 (50.00–75.00)	79.00 (63.00–89.75)*	74.00 (64.00–85.00)*	<0.001
R4	64.00 (50.00–77.00)	60.00 (48.00–72.00)	78.00 (60.00–92.00)*	70.00 (62.00–80.00)*	<0.001
R5	52.00 (41.50–61.00)	49.00 (40.00–57.50)	60.00 (51.00–70.00)*	55.00 (50.00–66.50)*	<0.001
The level of PIFR					<0.01
Insufficient	179 (33.6)	144 (38.5)	21 (22.1)*	14 (22.2)*	
Optimal	240 (45.1)	159 (42.5)	46 (48.4)	35 (55.6)	
Excessive	113 (21.3)	71 (19.0)	28 (29.5)	14 (22.2)	

Data are presented as the medians (IQRs) or numbers (%).
*Compared with the COPD group.
†Compared with the asthma group.
ACO, asthma-COPD overlap; COPD, chronic obstructive pulmonary disease; PIFR, peak inspiratory flow rate.

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Table 4 Results of the multivariate logistic regression: variables that were significantly associated with poor concordance to inhalers (test of adherence to inhalers-10≤45) in the total population and disease subgroups

	Total sample (n=532)		COPD group (n=374)		Asthma group (n=95)		ACO group (n=63)	
Variable	Crude OR (95% CI)‡	Adjusted OR (95% CI)	Crude OR (95% CI)‡	Adjusted OR (95% CI)	Crude OR (95% CI)‡	Adjusted OR (95% CI)	Crude OR (95% CI)‡	Adjusted OR (95% CI)
Sex (male vs female)	1.66 (1.07 to 2.60)	1.20 (0.47 to 3.03)	–	–	–	–	–	–
Educational level (primary vs secondary school and above	–	–	0.62 (0.39 to 0.98)	0.78 (0.44 to 1.38)	–	–	–	–
Smoking status (smoker vs non-smoker)	1.51 (1.01 to 2.26)	0.92 (0.48 to 1.78)	–	–	–	–	–	–
Medication time (years)	0.93 (0.88 to 0.99)	0.96 (0.90 to 1.03)	0.90 (0.83 to 0.97)	0.93 (0.85 to 1.03)	–	–	–	–
Disease diagnosis			–	–	–	–	–	–
COPD	1.00 (reference)	1.00 (reference)						
Asthma	1.80 (1.15 to 2.80)	1.26 (0.70 to 2.28)						
ACO	1.59 (0.87 to 2.88)	1.99 (0.96 to 4.13)						
CAT score	–	–	–	–	–	–	1.13 (1.01 to 1.26)	1.13 (1.01 to 1.26)*
ACT score	–	–	–	–	0.82 (0.70 to 0.95)	0.82 (0.70 to 0.95)**	–	–
Medication (mono/dual combination therapy vs triple therapy)†	0.59 (0.40 to 0.85)	0.60 (0.35 to 0.86) **	0.59 (0.37 to 0.92)	0.47 (0.27 to 0.80)**	–	–	–	–
Inhalation device (single vs multiple)	–	–	0.56 (0.33 to 0.95)	0.94 (0.40 to 2.20)	–	–	–	–
PIFR (optimal vs suboptimal§)	1.55 (1.00 to 2.40)	1.61 (1.04 to 2.51)*	1.90 (1.12 to 3.23)	1.93 (1.12 to 3.31)*	–	–	–	–

*P value<0.05, **P<0.01, ***P<0.001.
†Triple therapy (ICS/LABA/LAMA) included open triple and fixed triple therapy. Monotherapy refers to LAMA. Dual therapy included ICS/LABA and LABA/LAMA.
‡Only patient covariates that were significant in bivariate analyses with the primary predictor of interest (p<0.05) were included in the final model.
§Suboptimal PIFR was defined as excessive and insufficient PIFR.
ACO, asthma-COPD overlap; ACT, asthma control test; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; LABA, long-acting beta-adrenoceptor agonist; LAMA, long-acting muscarinic receptor antagonist; PIFR, peak inspiratory flow rate.

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Table 5 Results of the multivariate logistic regression: variables that were significantly associated with insufficient PIFR in the total population and disease subgroups

	Total sample (n=532)		COPD group (n=374)		Asthma group (n=95)		ACO group (n=63)	
Variable	Crude OR (95% CI)†	Adjusted OR (95% CI)	Crude OR (95% CI)†	Adjusted OR (95% CI)	Crude OR (95% CI)†	Adjusted OR (95% CI)	Crude OR (95% CI)†	Adjusted OR (95% CI)
Age (years)	1.06 (1.03 to 1.08)	1.05 (1.01 to 1.08) *			1.08 (1.01 to 1.15)	1.10 (1.01 to 1.20)*	–	–
Body mass index (kg/m^2)	0.89 (0.84 to 0.96)	0.96 (0.87 to 1.06)	0.87 (0.81 to 0.95)	0.93 (0.83 to 1.04)	–	–	–	–
Educational level (primary vs secondary school and above)	0.38 (0.24 to 0.61)	0.54 (0.28 to 1.01) *	0.37 (0.22 to 0.65)	0.41 (0.20 to 0.85)*	0.17 (0.04 to 0.68)	0.61 (0.11 to 3.43)	–	–
Smoking status (smoker vs non-smoker)	0.58 (0.34 to 1.00)	2.44 (1.05 to 5.70)	–	–	–	–	–	–
The history of severe exacerbations in the past year (no vs yes)	2.43 (1.54 to 3.83)	1.60 (0.84 to 3.03)	2.15 (1.26 to 3.66)	2.10 (1.03 to 4.32)*	–	–	–	–
Years since diagnosis	–	–	–	–	1.10 (1.01 to 1.18)	1.12 (1.02 to 1.24)*	–	–
Disease diagnosis			–	–	–	–	–	–
COPD	1.00 (reference)	1.00 (reference)						
Asthma	0.26 (0.13 to 0.52)	0.50 (0.12 to 2.03)						
ACO	0.50 (0.24 to 1.06)	0.40 (0.15 to 1.09)						
CAT score	–	–	1.05 (1.01 to 1.10)	0.99 (0.93 to 1.07)	–	–	–	–
mMRC dyspnoea grade	–	–	1.58 (1.19 to 2.11)	1.40 (0.95 to 2.07)	–	–	–	–
Inhalation device (DPIs† vs pMDIs/SMI)	0.12 (0.03 to 0.40)	0.15 (0.04 to 0.55)**	0.14 (0.04 to 0.47)	0.18 (0.05 to 0.67)*	–	–	–	–
Inhalation device (single vs multiple)	2.67 (1.56 to 4.57)	1.77 (0.84 to 3.74)	–	–	–	–	6.13 (1.33 to 28.20)	18.74 (0.74 to 475.10)

Continued

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Table 5 Continued

Variable	Total sample (n=532)		COPD group (n=374)		Asthma group (n=95)		ACO group (n=63)	
	Crude OR (95% CI)†	Adjusted OR (95% CI)	Crude OR (95% CI)†	Adjusted OR (95% CI)	Crude OR (95% CI)†	Adjusted OR (95% CI)	Crude OR (95% CI)†	Adjusted OR (95% CI)
FEV_1% predicted	0.97 (0.96 to 0.99)	0.97 (0.96 to 0.99)***	0.97 (0.96 to 0.99)	0.98 (0.96 to 1.00)*	–	–	0.89 (0.81 to 0.98)	0.85 (0.72 to 1.00)*
stable vs exacerbation	3.41 (2.14 to 5.43)	1.35 (0.62 to 2.96)	2.63 (1.54 to 4.50)	1.18 (0.53 to 2.65)				
GOLD group (A and B vs C and D)	–	–	1.96 (1.14 to 3.37)	0.65 (0.10 to 4.20)	–	–	–	–

*P value<0.05, **P<0.01, ***P<0.001.
†DPIs, DPIs+DPIs and DPIs+SMIs were included.
‡Only patient covariates that were significant in bivariate analyses with the primary predictor of interest (p<0.05) were included in the final model.
ACO, asthma-COPD overlap; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; DPIs, dry powder inhalers; FEV_1, forced expiratory volume in 1 s; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council; PIFR, peak inspiratory flow rate; pMDIs, pressurised metred-dose inhalers; SMIs, Respimat soft mist inhalers.

inhaler concordance and persistence compared with the use of multiple inhalers.[33–36] Combined with the findings of previous studies, our results may be explained by the high percentage of patients who developed better outcomes with SITT than with mono-/dual combination therapy.[37] Accordingly, healthcare professionals should pay more attention to follow-up and concordance assessment among patients with COPD with suboptimal PIFR and mono/dual combination therapy.

Overall, 54.9% of patients exhibited suboptimal PIFR, suggesting that many patients cannot generate appropriate PIFR, which might lead to treatment failure. Multivariate regression analysis revealed that four independent variables including older age, lower educational level, use of DPIs and lower FEV_1% predicted were associated with insufficient PIFR in all patients. The PIFR is inversely correlated with the internal resistance of inhalation devices.[15 20] DPIs have greater resistance than pMDIs (no resistance) and are prone to result in lower and even insufficient PIFR. Although there was no linear relationship between the PIFR and FEV_1,[18 29] our study observed a greater proportion of insufficient PIFR in patients with lower FEV_1% predicted. These results suggested that healthcare professionals should assess PIFR in Chinese patients with chronic airway diseases, especially in older patients with lower educational levels, worse lung function and use of DPIs.

Not only educational level, inhalation devices and FEV_1% predicted but also the history of severe exacerbations in the past year was an important predictor of insufficient PIFR in patients with COPD. This may be because inspiratory muscle strength has difficulty completely recovering to a normal degree after serious exacerbations of COPD, leading to insufficient PIFR.[38 39] In addition, our study indicated that patients with COPD presented a greater proportion of insufficient PIFR than did patients with asthma and patients with ACO, which might be attributed to older age, worse lung function and severe air trapping among patients with COPD.[28 40 41] These results demonstrated that it might be more difficult for patients with COPD to overcome internal resistance to inhalation devices and thus obtain unsatisfactory and ineffective treatment outcomes.

One previous study assessed the difference in PIFR between patients with AECOPD and patients with COPD with stable status and indicated no significant difference between the two groups.[29] However, our study revealed that the PIFRs of patients with COPD were lower during acute exacerbation than during a stable status. This contradiction may be due to the different study populations and the heterogeneity of people. The former is a comparison of two groups of people with different states, while the latter is a comparison of different states in a group of people. In addition, there was a larger sample size and a higher proportion of patients in GOLD stages 3 and 4 (58.8%) in our study. Due to hyperinflation and hypoxaemia, respiratory muscles are more fatigued and muscle function is often more compromised in

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patients with AECOPD than in patients with COPD with a stable status,[19] resulting in a lower PIFR in patients with AECOPD. Deteriorative PIFR due to AECOPD might not satisfy the requirements of current inhalation devices and lead to ineffective inhaled therapy. In addition, multivariate regression analysis revealed that the use of DPIs and a lower FEV1% predicted were independent predictors of insufficient PIFR in patients with AECOPD. Therefore, we suggest that patients with AECOPD, especially those with worse lung function and those in groups C and D, should receive a PIFR assessment to determine the optimal inhalation device during exacerbation. On the other hand, nebulisation may rapidly and effectively alleviate symptoms in patients who are unable to measure PIFR for various reasons during exacerbation and therefore cannot determine their optimal inhalation device.[23 42]

Similar to previous studies,[43] our results showed that the PIFR was negatively associated with age and years since diagnosis among patients with asthma. For patients with ACO, a lower FEV_1% predicted was the only and strongest determinant of insufficient PIFR. Accordingly, caution should be taken among older patients with asthma with a longer course of disease and patients with ACO with GOLD stages 3 and 4 because they may benefit more from PIFR-optimisation of inhaler choice. It should be noted that the sample sizes in the exacerbation group and GOLD stages 3 and 4 groups of patients with asthma were too small to compare the difference in the PIFR between each asthma subgroup. Similarly, despite a higher percentage of insufficient PIFR in the exacerbation group than in the stable group among patients with ACO, the difference was not statistically significant, which might be due to the small sample size.

There were some limitations in this study. First, the main limitation was utilisation of self-reported questionnaire to assess inhaler concordance. The authors considered that using a self-reported questionnaire was the better option for study design and aim since it is simple and flexible for clinicians, although it can under-report non-concordance. In the corresponding literature, there is an abundance of concordance questionnaires, however, in our study, the chosen questionnaire was TAI because of its specialisation in chronic airway diseases. Further studies should combine self-reports with objective measurements of concordance (eg, prescription refills) to determine inhaler concordance. Furthermore, a larger sample size is needed to observe the characteristics in subgroups of patients with asthma and patients with ACO. In addition, we will determine whether PIFR-optimisation of inhaler choice can improve clinical outcomes in a future prospective study.

CONCLUSIONS

Our study revealed that patients' inhaler concordance was low and that suboptimal PIFR was a noticeable risk factor for poor concordance among Chinese patients with chronic airway diseases. To improve inhaler concordance and clinical outcomes, PIFR assessment could be performed for patients with chronic airway diseases, especially for those at high risk of insufficient PIFR. In addition, the PIFR should be assessed in patients with AECOPD to choose an appropriate inhalation device.

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