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ORIGINAL RESEARCH

Patterns and Adherence to GOLD-Recommended Inhaled Therapy in Chronic Obstructive Pulmonary Disease (COPD) Patients with Acute Exacerbation History in Primary Care in China

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Purpose: The standardized treatment of chronic obstructive pulmonary disease (COPD) in primary care settings in China remains suboptimal. This study aims to investigate the inhaled medication patterns among COPD patients with a history of acute exacerbations in primary care settings and to analyze the prescription adherence of inhaled medication for those COPD patients to the Global Strategy for Prevention, Diagnosis and Management of COPD (2023).

Patients and methods: A cross-sectional analysis of the baseline data from a multicenter, prospective cohort of COPD participants was performed. Patients diagnosed with COPD and had at least one mild, moderate or severe acute exacerbation in the previous 12 months were enrolled from 12 primary care clinics in two cities in China (Beijing and Chengdu). Sociodemographic information, symptoms and quality of life, pulmonary function results and inhaled therapy types were collected. Inhaled therapy distributions and adherence to GOLD recommendations were described and visualized, proportions were summarized descriptively.

Results: Six hundred and forty-six participants were included in the analysis. 82.7% of the patients were men, mean age 68.7 years. Group A, B, and E accounted for 12.1%, 13.7%, and 66.1%, respectively. 33.4% of the participants received No inhaled therapy. The most frequently used regimen was LABA/ICS (29.9%), followed by LABA/LAMA/ICS (26.0%). Adherence to GOLD strategy was the lowest in group B (4.2%), highest in group E (33.5%). Based on GOLD 2023 recommendation, 35.3% of the group A participants and 32.3% of the group B participants showed inhaled medication underuse, whereas 55.3% and 63.5% showed inhaled medication overuse in group A and B, respectively.

Conclusion: Among the COPD patients with a history of acute exacerbations at primary care, prescribing frequently diverged from GOLD 2023 recommendations, characterized by high rates of No inhaled therapy and widespread use of ICS-containing regimens in groups A and B, necessitating improved prescription guideline adherence in the future to facilitate the implementation of standardized COPD management.

Keywords: chronic obstructive pulmonary disease, primary care cohort, inhaled therapy, prescription patterns, guideline adherence

Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous chronic respiratory disease characterized by persistent, and often progressive airflow obstruction which causes chronic respiratory symptoms such as dyspnea, cough, sputum production.[1] COPD poses an enormous burden worldwide, ranking 4th among global causes of death,[2] with the economic burden worldwide reaching approximately $144.2 billion annually.[3] COPD is an important chronic respiratory disease in

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China. The prevalence of COPD among people over 40 years of age has reached 13.7%, and the number of patients among those over 20 years of age is nearly 100 million.[4] Acute exacerbations are the main reasons for hospitalization of COPD patients. Acute exacerbations occur at a frequency of 0.5–3.5 episodes per patient annually,[5] with the associated inpatient costs amounting to approximately 11,598 RMB (approximately 1,625 USD) per patient per year.[6]

Effective management of COPD, especially in primary care settings, is crucial for improving patient outcomes and reducing the burden of the disease. In September 2024, China included COPD in the National Basic Public Health Services Program, marking a national emphasis on this disease, and bringing it to the same status as hypertension and diabetes.[7] This measure requires the implementation of a tiered diagnosis and treatment system, providing comprehensive management services such as screening, diagnosis, pharmacological and non-pharmacological treatment, follow-up management, and functional rehabilitation for high-risk and diagnosed COPD patients to improve the early diagnosis, treatment rates, and standardized management of COPD at the primary care level.[8] The rational use of medication, timely use of appropriate drugs based on symptoms and acute exacerbation, is an important part of achieving these goals in COPD patients.[8]

Inhaled therapy is a cornerstone in COPD management, especially for patients with exacerbation history. Evidence shows that appropriate use of inhaled therapy reduces exacerbations, controls respiratory symptoms, improves lung function and may also reduce all-cause mortality in COPD patients.[9–11] As research on COPD increases, chapters concerning COPD management in the Global Strategy for Prevention, Diagnosis and Management of COPD (GOLD) have been updated continuously in recent years. In the GOLD 2023 report, the previous classification of groups A, B, C and D groups were merged into groups A, B and E, emphasizing the risk of acute exacerbations in guiding the use of medications.[1] In addition, according to recent evidence, GOLD has gradually narrowed the indications for inhaled corticosteroids/long-acting beta agonists (LABA/ICS), with groups B and E recommended to start with Long-acting beta agonists and long-acting muscarinic antagonist (LABA/LAMA) and only recommend LABA/LAMA/ICS when EOS≥300/μL in group E patients. This change seeks to balance the benefits of LABA/LAMA/ICS including further reduction in exacerbation, improvement in lung function and symptoms,[10] with potential risks of adverse reactions of ICS such as pneumonia, glucose metabolism disorders.[1]

Despite the availability of recommendations and guidelines, the standardized treatment of COPD in primary care settings in China remains suboptimal.[12–15] The gap between guideline and real-world drug use is shown by prescription guideline adherence. Assessment of prescription guideline adherence commonly uses the proportion of prescription practices consistent with guidelines and the incidence of inappropriate medication as indicators.[16] Previous researches demonstrated that there are significant disparities in the capacity of primary care in China to diagnose and manage respiratory diseases,[17] with the eastern regions outperforming the western regions, and no unified COPD management standard has been implemented yet.

In 2021, to promote a primary care-centered tiered COPD management model and explore integration with proactive health technology, Peking University First Hospital established a prospective multicenter cohort of COPD patients.[18] On the basis of previous research experience, 12 community health care centers in Beijing and Chengdu were chosen as research sites, representing two regions in China with a high prevalence of COPD (southwest and north)[19–21] and the current status of primary care in the east and west.[17] Based on the baseline data, this study aims to describe the current patterns of inhaled pharmacotherapy among COPD patients with a history of acute exacerbations in primary care settings in China. It also seeks to analyze the prescription guideline adherence of inhaled medications to the GOLD 2023 strategy. This information will provide valuable insights for improving the rational use of inhaled therapies and promoting standardized COPD management in primary care in China.

Methods

Study Design and Participants

This study is a cross-sectional analysis of the baseline data of a prospective, multicenter, community-based cohort which is established to develop prediction models for COPD exacerbation using proactive health technologies (Chinese Clinical Trial Registry (www.chictr.org.cn): ChiCTR2500108349). Details of the design of the underlying cohort study have been described elsewhere previously.[18] Briefly, between October 2023 and June 2025, 820 participants reported to have COPD diagnosis from 12 community health service centers (6 in Beijing and 6 in Chengdu) were recruited, ultimately, 704 stable COPD patients

who met the inclusion and did not meet the exclusion criteria were enrolled in the cohort. Patients inclusion criteria: age 40–80 years; physician diagnosed stable COPD according to the 2023 Chinese COPD Guidelines; ≥1 exacerbation in the previous 12 months (defined as worsening of respiratory symptoms, requirement for systemic corticosteroids or antibiotics, or hospitalization). Main exclusion criteria: other chronic respiratory disorders that could impair lung function (eg, asthma, active lung cancer, active tuberculosis, bronchiectasis); severe comorbidities such as malignant tumours or chronic heart failure; pregnancy. Detailed inclusion and exclusion criteria were shown in the protocol.[18]

To be included in the present analysis, the patients with complete exacerbation records were included, with no other exclusion criteria beyond those of the underlying cohort. Only baseline data were analyzed in this study.

Data Collection

The data of the present cross-sectional analysis were obtained from the REDCap database of the underlying cohort's baseline data. The following procedures describe how baseline data were originally obtained in the cohort study. Baseline data contain: (1) questionnaire surveys, (2) spirometry test results.[18] Basic sociodemographic and anthropometric data (sex, age, height, weight, health-insurance type, education, employment, smoking status (never, former, current) and pack-year smoking history), COPD-specific symptom scores (modified Medical Research Council (mMRC), COPD Assessment Test (CAT)), exacerbations in the previous 12 months and quality of life (St George's Respiratory Questionnaire, SGRQ), were collected by trained interviewers using standardized questionnaires. Spirometry was performed by trained physicians at enrollment to confirm the diagnosis of COPD based on post-bronchodilator $FEV_1/FVC < 0.70$ and results were recorded. Comorbidities and inhaled therapy (class and dose) were collected from primary care electronic health records and self-reports. Inhaled therapies were classified hierarchically into six ascending levels according to pharmacological regimen complexity (low to high) rather than guideline preference or treatment appropriateness: (1) No inhaled therapy, (2) Short-acting beta agonists (SABA) or short-acting muscarinic antagonist (SAMA), (3) LABA or LAMA, (4) LABA/LAMA, (5) LABA/ICS, and (6) LABA/LAMA/ICS. When multiple classes were reported by participants, the highest level was assigned. This ordering was intended as an operational framework to facilitate descriptive comparison of inhaled therapy patterns in real-world primary care practice. Data were uploaded and stored in the REDCap database. The data management personnel from the research group performed verification on all uploaded data to ensure its integrity and accuracy.

Outcomes

The primary objective of this study was to characterize the study population's inhaled pharmacotherapy patterns and compare them with GOLD 2023 recommendations. Participants were stratified into GOLD groups A, B and E using baseline CAT score and exacerbation history. Per GOLD 2023, the initiation recommendations for inhaled therapy are as follows:

- Group A: one bronchodilator (SABA or SAMA, or LABA or LAMA) is recommended.
- Group B: LABA/LAMA is recommended.
- Group E: LABA/LAMA or LABA/LAMA/ICS (if blood eosinophils ≥300 cells/μL) is recommended.

Guideline adherence was defined as concordance between the baseline inhaled regimen and the corresponding GOLD 2023 recommendation. Because blood eosinophil counts were not available during the data collection process, the use of either LABA/LAMA or LABA/LAMA/ICS in group E was considered guideline adherent. Non-adherence was further classified into inhaled medication overuse and inhaled medication underuse. These terms refer to deviations from GOLD strategy recommendations and do not indicate clinical inappropriateness in individual patients. Inhaled medication overuse was defined as (1) group A receiving both long-acting bronchodilators or any ICS-containing regimen or (2) group B receiving an ICS-containing regimen. Inhaled medication underuse was defined as (1) No inhaled therapy; (2) group B receiving only one bronchodilator; or (3) group E receiving only one bronchodilator or LABA/ICS.[16] The operational definitions are summarized in Table 1.

Table 1 Operational Definitions of Guideline Adherence, Inhaled Medication Underuse, and Inhaled Medication Overuse

	Guideline Adherence	Inhaled Medication Underuse	Inhaled Medication Overuse
A	SABA or SAMA, LABA or LAMA	No inhaled therapy	LABA/LAMA, LABA/ICS, LABA/LAMA/ICS
B	LABA/LAMA	No inhaled therapy, SABA or SAMA, LABA or LAMA	LABA/ICS, LABA/LAMA/ICS
E	LABA/LAMA, LABA/LAMA/ICS*	No inhaled therapy, SABA or SAMA, LABA or LAMA, LABA/ICS	/

Notes: *Because blood eosinophil counts were not available in data collection process, use of either LABA/LAMA or LABA/LAMA/ICS in group E was considered guideline adherent.

Statistical Analysis

Descriptive statistics were used to characterize the study population overall and by GOLD group. Inhaled therapy patterns and the prescription guideline adherence were described within each GOLD group. Among patients with and without prescription guideline adherence, we further compared the proportion of patients reporting persistent respiratory symptoms, CAT scores and SGRQ scores.

Continuous variables are presented as means (SD); categorical variables are presented as numbers (percentages). Categorical variables and proportions were compared using the Pearson's chi-square test or the likelihood ratio chi-square test when appropriate. Normality of continuous variables was assessed with the Shapiro–Wilk test; normally distributed data were compared with one-way ANOVA; otherwise they were compared with the Kruskal–Wallis *H*-test. A two-sided p value <0.05 was considered statistically significant. The post-hoc comparisons for categorical variables used the chi-square test or the Fisher's exact test when appropriate, and Tukey's HSD test or the Mann–Whitney *U*-test for continuous variables; the p value was adjusted via the Bonferroni correction. All data analyses processes were conducted using Python 3.10.4.

Ethics Approval and Informed Consent

The study protocol was approved by the ethics review committee of Peking University First Hospital (approval number: 2022Research513-001). Written informed consent was obtained from all participating patients, and all study processes were performed in compliance with the Declaration of Helsinki and Good Clinical Practice.

Results

Patients Characteristics

A total of 646 participants were included in the analysis. The study population was predominantly older men (n = 534, 82.7%), with a mean age of 68.8 years (Table 2). The proportion of participants whose body-mass index (BMI) was within the healthy weight range is 55.4%, in that of underweight (<18.5 kg/m^2) is 4.5%, and overweight (≥25 kg/m^2) in 40.1%. Almost all participants had health insurance: 51.9% were covered by urban employee medical insurance, 44.6% by urban-rural resident insurance, 2.6% by public-funded medical care, and 0.9% paid out-of-pocket; none of the patients reported to have commercial insurance. Education level was generally low: 57.9% had completed junior high school or less (primary or below 20.9%, junior high 37.9%), 22.8% senior high/technical secondary, and 18.4% college or above. Participants' employment status was mainly retired (39.5%), followed by farmers (22.8%) and manual workers (18.4%). Current-smoker was reported by 43.2%, former-smoker by 31.9%, and never-smoker by 24.9%. The mean pack-year smoking history was 25.7. Comorbidities were common, most frequently reported were cardiovascular and metabolic disorders. Hypertension was reported in 48.6% of the participants, diabetes in 20.6%, and ischemic heart disease in 12.5%. Overall, 36.2% participants had no comorbidity; 35.0%, 18.6%, and 10.2% had one, two, or three or more comorbidities, respectively.

The participants in the study population had a mean duration of COPD of 5.1 years (SD = 6.6) (Table 3). Reported symptoms were predominantly cough (63.5%), sputum production (60.8%), and wheeze (40.8%). Overall, 32.9% of participants had an mMRC score ≥2, and more than half (54.0%) had a CAT score ≥10. Regarding exacerbations, in the preceding 12 months, 41.4% of the participants experienced one exacerbation, 39.3% experienced two, 11.1%

Table 2 Sociodemographic Characteristics of the Participants

Characteristics	Total (N = 646)	GOLD Group A (n = 85)	GOLD Group B (n = 96)	GOLD Group E (n = 465)
Sex, n (%)				
Male	534 (82.7%)	73 (85.9%)	74 (77.1%)	387 (83.2%)
Female	112 (17.3%)	12 (14.1%)	22 (22.9%)	78 (16.8%)
Age (years), mean (SD)	68.8 (6.4)	66.8 (7.0)	69.0 (6.0)	69.1 (6.4)
BMI (kg/m^2), mean (SD)	24.3 (3.6)	24.7 (3.2)	24.4 (3.8)	24.2 (3.6)
BMI category (kg/m^2), n (%)				
Underweight (<18.5)	29 (4.5%)	2 (2.4%)	6 (6.2%)	21 (4.5%)
Normal weight (18.5–24.9)	358 (55.4%)	44 (51.8%)	49 (51%)	265 (57%)
Overweight (>25.0)	259 (40.1%)	39 (45.9%)	41 (42.7%)	179 (38.5%)
Insurance type, n (%)				
Urban-rural resident basic medical insurance	288 (44.6%)	35 (41.2%)	45 (46.9%)	208 (44.7%)
Employee/Provincial government medical insurance	335 (51.9%)	43 (50.6%)	46 (47.9%)	246 (52.9%)
Commercial insurance	0	0	0	0
Public-funded medical care	17 (2.6%)	5 (5.9%)	4 (4.2%)	8 (1.7%)
Self-pay	6 (0.9%)	2 (2.4%)	1 (1.0%)	3 (0.6%)
Education level, N (%)				
Primary school or below	135 (20.9%)	12 (14.1%)	28 (29.2%)	95 (20.4%)
Middle school (junior high)	245 (37.9%)	33 (38.8%)	33 (34.4%)	179 (38.5%)
High school/Vocational school	147 (22.8%)	25 (29.4%)	20 (20.8%)	102 (21.9%)
College/Associate degree	109 (16.9%)	14 (16.5%)	14 (14.6%)	81 (17.4%)
Postgraduate or above	10 (1.5%)	1 (1.2%)	1 (1.0%)	8 (1.7%)
Occupation, N (%)				
Retired	255 (39.5%)	29 (34.1%)	32 (33.3%)	194 (41.7%)
Worker	119 (18.4%)	17 (20.0%)	16 (16.7%)	86 (18.5%)
Farmer	147 (22.8%)	14 (16.5%)	22 (22.9%)	111 (23.9%)
Other	125 (19.3%)	25 (29.4%)	26 (27.1%)	74 (15.9%)
Smoking status, N (%)				
Never smoker	161 (24.9%)	21 (24.7%)	30 (31.2%)	110 (23.7%)
Former smoker	206 (31.9%)	24 (28.2%)	30 (31.2%)	152 (32.7%)
Current smoker	279 (43.2%)	40 (47.1%)	36 (37.5%)	203 (43.7%)
Smoking, pack-year, mean (SD)	25.7 (25.4)	26.1 (26.9)	28.9 (33.7)	25.0 (23.0)
Comorbidity N (%)				
Ischemic heart disease	81 (12.5%)	13 (15.3%)	9 (9.4%)	59 (12.7%)

(*Continued*)

Table 2 (Continued).

Characteristics	Total (N = 646)	GOLD Group A (n = 85)	GOLD Group B (n = 96)	GOLD Group E (n = 465)
Cardiac arrhythmia	34 (5.3%)	1 (1.2%)	7 (7.3%)	26 (5.6%)
Peripheral vascular disease	5 (0.8%)	1 (1.2%)	1 (1.0%)	3 (0.6%)
Hypertension	314 (48.6%)	37 (43.5%)	44 (45.8%)	233 (50.1%)
Obstructive sleep apnea	13 (2.0%)	0	2 (2.1%)	11 (2.4%)
Osteoporosis	62 (9.6%)	5 (5.9%)	15 (15.6%)	42 (9%)
Anxiety/Depression	17 (2.6%)	2 (2.4%)	0	15 (3.2%)
Diabetes mellitus	133 (20.6%)	17 (20.0%)	18 (18.8%)	98 (21.1%)
Gastroesophageal reflux disease	37 (5.7%)	0	4 (4.2%)	33 (7.1%)
Number of comorbidities, n (%)				
0	234 (36.2%)	39 (45.9%)	38 (39.6%)	157 (33.8%)
1	226 (35.0%)	21 (24.7%)	32 (33.3%)	173 (37.2%)
2	120 (18.6%)	21 (24.7%)	16 (16.7%)	83 (17.8%)
≥3	66 (10.2%)	4 (4.7%)	10 (10.4%)	52 (11.2%)

Table 3 Clinical Characteristics of the Participants

Characteristics	Total (N = 646)	GOLD Group A (n = 85)	GOLD Group B (n = 96)	GOLD Group E (n = 465)
Time since COPD diagnosis (years), mean (SD)	5.1 (6.6)	4.2 (5.2)	5.3 (6.5)	5.3 (6.8)
COPD signs and symptoms, n (%)				
Dyspnea	179 (27.7%)	12 (14.1%)	24 (25.0%)	143 (30.8%)
Cough	410 (63.5%)	42 (49.4%)	59 (61.5%)	306 (66.5%)
Sputum	393 (60.8%)	35 (41.2%)	61 (63.5%)	297 (63.9%)
Wheeze	265 (41.0%)	20 (23.5%)	40 (41.7%)	205 (44.1%)
Chest tightness	171 (26.5%)	13 (15.3%)	26 (27.1%)	132 (28.4%)
mMRC, n (%)				
0	194 (30.0%)	48 (56.5%)	22 (22.9%)	124 (26.7%)
1	240 (37.2%)	25 (29.4%)	36 (37.5%)	179 (38.5%)
2	153 (23.7%)	11 (12.9%)	28 (29.2%)	114 (24.5%)
3	51 (7.9%)	1 (1.2%)	9 (9.4%)	41 (8.8%)
4	7 (1.1%)	0	1 (1.0%)	6 (1.3%)
Missing	1 (0.2%)	0	0	1 (0.2%)

(*Continued*)

Table 3 (Continued).

Characteristics	Total (N = 646)	GOLD Group A (n = 85)	GOLD Group B (n = 96)	GOLD Group E (n = 465)
CAT, n (%)				
<10	297 (46.0%)	85 (100%)	0	212 (45.6%)
≥10	349 (54.0%)	0	96 (100%)	253 (54.4%)
Number of exacerbations in previous 12 months				
1	267 (41.4%)	85 (100%)	96 (100%)	86 (18.5%)
2	254 (39.3%)	0	0	254 (54.6%)
3	72 (11.1%)	0	0	72 (15.5%)
≥4	53 (8.2%)	0	0	53 (11.4%)
Had severe exacerbation(s) in previous 12 months	153 (23.7%)	0	0	153 (100%)
Severity of airflow limitation (GOLD 2023), n(%)				
1	162 (25.1%)	26 (30.6%)	23 (24.0%)	113 (24.3%)
2	296 (45.8%)	44 (51.8%)	35 (36.5%)	217 (46.7%)
3	158 (24.5%)	14 (16.5%)	32 (33.3%)	112 (24.1%)
4	30 (4.6%)	1 (1.2%)	6 (6.2%)	23 (4.9%)
SGRQ, mean (SD)	27.3 (17.8)	13.2 (9.6)	33.3 (15.6)	28.7 (18.2)
SGRQ symptom	32.5 (21.6)	16.9 (14.6)	41.1 (20.3)	33.6 (21.5)
SGRQ activity	39.1 (21.9)	23.6 (16.6)	44.7 (20.1)	40.7 (22.0)
SGRQ impact	18.9 (18.7)	6.1 (8.1)	24.3 (17.9)	20.2 (19.2)

experienced three, and 8.2% experienced ≥4. Severe exacerbations within the prior year were reported by 23.7% of participants. By GOLD 2023, airflow limitation was predominantly mild to moderate: grades 1, 2, 3, and 4 accounted for 25.1%, 45.8%, 24.5%, and 4.6%, respectively. Health-related quality of life impairment was modest, with a mean SGRQ total score of 27.3 ± 17.8 (Table 3).

Stratified by the GOLD 2023 group, the study population was mainly composed of group E, with 85 (13.1%) in group A, 96 (14.9%) in group B, 465 (72.0%) in group E (Tables 2 and 3). Age, BMI, and the distributions of sex, education level, insurance category, occupation and smoking status were broadly similar across groups (Table 2). The distributions of the comorbidities and the number of comorbidities were similar. Common symptoms reporting appeared to differ across groups, with group A participants reporting persistent respiratory symptoms less commonly (Table 3). No hypothesis testing was performed.

Health-related quality of life also varied across groups (Table 3). The SGRQ total score was numerically lower, indicating better quality of life, in group A (13.2 ± 9.6) participants than in group B (33.3 ± 15.6) or group E (28.7 ± 18.2) participants; the same pattern was observed for each SGRQ domain (symptoms, activity, impacts).

Inhaled Therapy Patterns

Overall, the use of the listed inhaled therapies was low; approximately one-third (33.4%) of the participants received No inhaled treatment (Table 4 and Figure 1). Among the different GOLD groups, the proportion of untreated patients was highest in group A (35.3%), lowest in group B (24.0%), and intermediate in group E (35.1%).

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Table 4 Inhaled Therapy Patterns Stratified by GOLD Groups

Inhaled Therapy Type	Total (n = 646)	GOLD Group A (n = 85)	GOLD Group B (n = 96)	GOLD Group E (n = 465)
No inhaled therapy	216 (33.4%)	30 (35.3%)	23 (24.0%)	163 (35.1%)
SABA or SAMA	18 (2.8%)	1 (1.2%)	5 (5.2%)	12 (2.6%)
LABA or LAMA	22 (3.4%)	7 (8.2%)	3 (3.1%)	12 (2.6%)
LABA/LAMA	29 (4.5%)	2 (2.4%)	4 (4.2%)	23 (4.9%)
LABA/ICS	193 (29.9%)	35 (41.2%)	36 (37.5%)	122 (26.2%)
LABA/ LAMA/ICS	168 (26.0%)	10 (11.8%)	25 (26.0%)	133 (28.6%)

The two most common treatment regimens were LABA/ICS (29.9%) and LABA/LAMA/ICS (26.0%) (Table 4 and Figure 1). LABA/ICS was the dominant choice in groups A and B, whereas LABA/LAMA/ICS predominated in group E. In group A to E, the proportion of participants receiving LABA/ICS declined, whereas the use of LABA/LAMA/ICS increased; both groups B and E presented higher rates of LABA/LAMA/ICS than did group A. LABA/LAMA dual bronchodilator was used infrequently in all the groups (Table 4 and Figure 1).

Adherence to GOLD-Recommended Inhaled Therapy

Prescription guideline adherence with the GOLD 2023 recommendations was generally low (Figure 1 and Table 5). When analyzed in the GOLD groups, guideline adherence was the lowest in group B patients (only 4.2%), followed by group A (9.4%), and group E (33.5%). Inhaled medication overuse was more common than underuse. A total of 35.3% of the group A participants and 32.3% of the group B participants exhibited inhaled medication underuse, whereas 55.3% and 63.5% of the participants exhibited overuse in group A and B, respectively, according to GOLD recommendations (Table 5).

Guideline Adherence and Symptom Reporting

We then compared the proportion of patients reporting persistent respiratory symptoms, CAT scores, and SGRQ scores among participants whose therapy was guideline adherent, inhaled medication underuse, or inhaled medication overuse (Table 5).

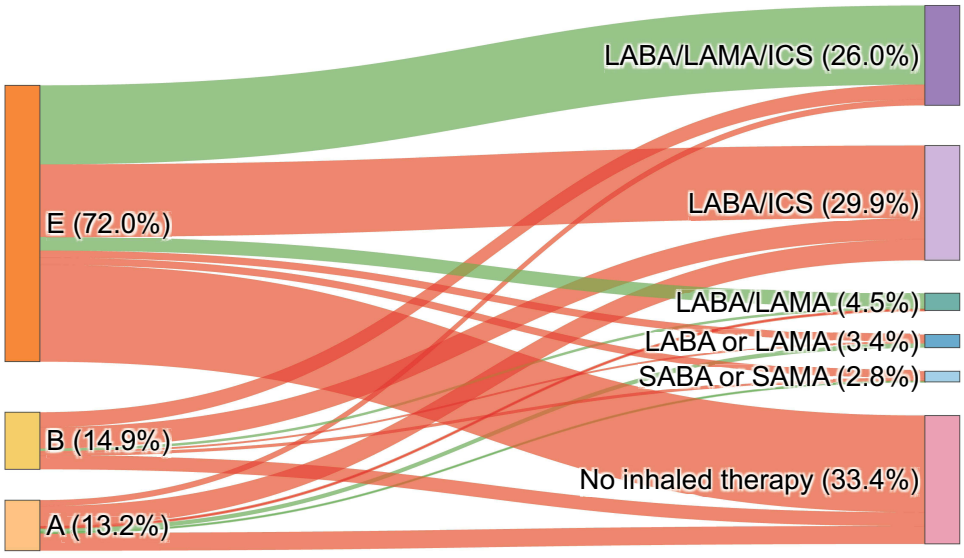

Figure 1 Sankey diagram of inhaled therapy patterns. The left bars show different GOLD groups (A, B, E), bar length indicates group size, and the right bars show inhaled therapy categories, bar length indicates users per therapy. The green links denote guideline-adherent therapies; red links denote non-adherent ones. Link thickness reflects the proportion using each therapy within the corresponding group.

Table 5 Comparison of Reported Persistent Respiratory Symptoms and Quality of Life Among Guideline Adherent Group, Inhaled Medication Underused Group and Inhaled Medication Overused Group

	Guideline Adherent	**Inhaled Medication Underused**	**Inhaled Medication Overused**	**P value**
GOLD group A (n = 85)	N = 8 (9.4%)	N = 30 (35.3%)	N = 47 (55.3%)	
Dyspnea	2 (25%)	4 (13.3%)	6 (12.8%)	0.688
Cough	3 (37.5%)	13 (43.3%)	26 (55.3%)	0.458
Sputum	2 (25%)	13 (43.3%)	20 (42.6%)	0.603
Wheezing	1 (12.5%)	4 (13.3%)	15 (31.9%)	0.117
Chest Tightness	4 (50%)	4 (13.3%)	5 (10.6%)	0.045
CAT	5.50 ± 2.00	4.53 ± 2.93	5.17 ± 2.74	0.575
SGRQ	14.59 ± 7.44	11.58 ± 9.38	13.96 ± 10.11	0.235
GOLD group B (n = 96)	N = 4 (4.2%)	N = 31 (32.3%)	N = 61 (63.5%)	
Dyspnea	1 (25%)	6 (19.4%)	17 (27.9%)	0.664
Cough	3 (75%)	22 (71.0%)	34 (55.7%)	0.303
Sputum	3 (75%)	19 (61.3%)	39 (63.9%)	0.856
Wheezing	1 (25%)	12 (38.7%)	27 (44.3%)	0.682
Chest Tightness	1 (25%)	6 (19.4%)	19 (31.1%)	0.470
CAT	12.50 ± 4.36	14.84 ± 4.57	17.05 ± 5.47	0.034
SGRQ	30.16 ± 2.21	28.71 ± 15.44	35.77 ± 15.72	0.070
GOLD group E (n = 465)	N = 156 (33.5%)	N = 309 (66.5%)	\	
Dyspnea	42 (26.9%)	101 (32.7%)	\	0.244
Cough	101 (64.7%)	208 (67.3%)	\	0.653
Sputum	94 (60.3%)	203 (65.7%)	\	0.293
Wheezing	75 (48.1%)	130 (42.1%)	\	0.257
Chest Tightness	46 (29.5%)	86 (27.8%)	\	0.791
CAT	11.50 ± 7.75	11.18 ± 7.01	\	0.894
SGRQ	30.05 ± 18.63	27.95 ± 17.90	\	0.282

In group A, no significant differences were detected across the three treatment categories in the proportion of patients reporting individual respiratory symptoms except for chest tightness. CAT and SGRQ scores also showed no significant differences. Chest tightness was more common in the guideline adherent group, and post-hoc analysis confirmed the result. Among group B participants, the proportion of patients reporting persistent respiratory symptoms did not differ across treatment groups. CAT scores differed between groups, but post hoc analysis did not reveal differences between any two groups after Bonferroni adjustment. In group E, neither the proportion of patients reporting persistent respiratory symptoms nor CAT or SGRQ scores differed between patients in guideline adherent group and those in inhaled medication underused group.

The detailed frequencies of reported respiratory symptoms and quality-of-life scores are presented in Table 5. Interpretation of these findings should be cautious for patients in group A and B because there were few guideline-adherent patients.

Discussion

This study delineates patterns and adherence to GOLD recommendations of inhaled therapies among participants from a multicentered cohort study in China. The findings indicate a high proportion of untreated patients within the cohort; among those treated, the LABA/ICS and LABA/LAMA/ICS regimens predominated. Across GOLD categories, prescription adherence to GOLD recommendations was uniformly low, especially in relatively milder patient groups.

The population of this study consisted of community-dwelling COPD patients with a history of acute exacerbations in the year preceding enrollment. The majority were GOLD stages 1–2, with group E accounting for the largest proportion (72.0%). Nearly a quarter experienced severe exacerbations during that period. Unlike prior studies, this analysis was established on the basis of China's primary care clinics and specifically targeted COPD patients with an exacerbation history in the preceding year.[12,22] Patients with a history of exacerbation require more attention to their treatment and guideline adherence may help their disease management.

Our results highlight the substantial underuse of inhaled therapies, with more than one-third of enrolled COPD patients receiving No inhaled treatment, even in relatively severe (group E) participants. The reported proportion of COPD patients who do not use inhaled medication varies across studies.[12,23] In the REAL study, only 15% of patients were not treated with regimens containing ICS or long-acting bronchodilator, likely reflecting their recruitment from secondary and tertiary hospitals where patients present with greater symptom burden and receive more intensive treatment.[12] In contrast, a study in Germany recruiting from both primary and secondary care reported that 65.4% of participants overall were not using regimens containing ICS or long-acting bronchodilators; even among patients with multiple or severe exacerbations, 36.8% remained untreated with these regimens, a proportion higher than that in our study.[23] In hospital settings, a study from a Chinese tertiary hospital reported that more than half of COPD patients were not using inhaled therapy.[13] By contrast, underuse of inhaled therapy appears to be less pronounced in some other countries. For example, a study conducted in Italy reported that approximately 9% of COPD patients were not using inhaled medications, while an Australian single-center study found that undertreatment relative to guideline recommendations persisted but varied by disease severity, ranging from approximately 10% to 17%.[24,25] Several factors may contribute to the underuse of inhaled therapies in real-world practice, including general practitioners' underestimation of the disease, patients' low awareness about COPD, delayed diagnosis and prescription, lack of social support, and economic burden.[12,24,26]

Overuse of inhaled therapy was also observed in the present study. More than half of the participants classified as GOLD groups A and B received inhaled regimens exceeding the recommendations of the GOLD strategy, which is consistent with findings from previous real-world studies. In hospital-based settings, an Australian study reported that approximately 47% of COPD patients were prescribed inhaled therapies considered to exceed guideline recommendations.[25] Similarly, a multicenter study by Case et al reported that over 85% of inappropriate inhaled medication use was attributable to prescriptions exceeding recommended treatment levels.[16] Several factors may underlie this pattern, including the influence of pharmaceutical marketing, medication efficacy demonstrated in clinical trials, and a preference for more intensive regimens to mitigate perceived clinical risk.[24] Additionally, in some healthcare settings, the greater availability of LABA/LAMA/ICS compared with dual bronchodilator regimens may further contribute to such prescribing practices.[24]

In this study, we defined ICS-containing regimens in GOLD groups A and B (including LABA/ICS and LABA/LAMA/ICS) as inhaled medication overuse, in line with the progressively more restrictive indications for the use of ICS in recent GOLD strategies. Historically, because both COPD and asthma both involve chronic airway inflammation, recommendations for the use of ICS in COPD patients were extrapolated from asthma research.[27] Subsequent investigations revealed that the inflammatory endotypes of COPD and asthma are different, implying that ICS are not universally beneficial for COPD patients and may be effective only in certain subgroups. A series of studies has refined the appropriate scope of ICS use in COPD patients. The IMPACT trial showed that, compared with LABA/LAMA, triple therapy (LABA/LAMA/ICS) significantly reduced exacerbations primarily among frequent exacerbators (≥2 moderate or ≥1 severe exacerbations) with blood eosinophil counts ≥300/μL, with limited benefit observed in patients with lower eosinophil counts.[28] In 2019, GOLD explicitly incorporated blood

eosinophils as a decision criterion for ICS initiation, recommending ICS use only in patients with frequent exacerbations, higher symptom burden, and elevated eosinophil counts.[1]

Consistent with prior studies, we observed that LABA/ICS was among the most frequently prescribed regimens: it was the most common in groups A and B (35.0% and 33.8%, respectively) and the second most common in group E (28.0%).[12,15,23,29] Historically, COPD treatment favored LABA/ICS. Early RCTs demonstrated that, compared with LABA monotherapy, LABA/ICS reduced exacerbation rates, slowed the decline in lung function, and improved quality of life.[30,31] The benefits appeared more pronounced in patients with severe airflow limitation (FEV1 < 50%),[30] with a non-significant trend toward lower all-cause mortality.[31] Subsequent analyses suggested that the observed benefits of the combination might be largely driven by the LABA component,[32] sustaining uncertainty regarding the incremental value of ICS in broad COPD populations.

As evidence has accumulated, GOLD recommendations have progressively deemphasized LABA/ICS for COPD patients without asthmatic features; GOLD 2023 explicitly advises against LABA/ICS in patients without concomitant asthma.[1] In line with this, the FLAME trial showed that among patients with a history of moderate-to-severe exacerbations (predominantly groups B and D), LAMA/LABA was superior to LABA/ICS in reducing exacerbations and was associated with a lower incidence of pneumonia.[33] Nonetheless, prescribing patterns in primary care appear to retain earlier treatment paradigms and have not been updated in a timely manner.

Mirroring the above, LABA/LAMA usage ranked behind LABA/ICS and LABA/LAMA/ICS in our cohort. Across all groups, only 2–4% of patients received LABA/LAMA. This was particularly notable in Group B, where despite guideline recommending LABA/LAMA as the first-line choice, most treated patients were escalated to ICS-containing regimens (LABA/ICS or LABA/LAMA/ICS). These findings align with the REAL cohort, in which only 0.7–1.7% of patients were on LABA/LAMA,[12] underscoring a gap between primary care physicians' prescription behavior with international guidelines.

Overall prescription adherence to the GOLD recommendations in our study was low (14.2%), showing no improvement compared with earlier findings. Prior community-based studies have reported wide variability in adherence (6.4%–35.5%),[15,34] likely reflecting differences in regional development and the specific guideline versions used in research as references. While adherence tends to be higher in hospital settings (29.7–59.5%),[22,29,35] it remains suboptimal, similar to other findings from high-income countries.[36,37] In particular, non-adherence was predominantly characterized by ICS over-prescription among patients with milder condition, similar to findings in the present study.[37]

Multiple factors may contribute to poor prescription adherence. First, in China, research shows that the leading reasons for nonadherence to clinical guidelines include a lack of training (46.2%) and overly broad guideline recommendations (43.8%).[38] Against the backdrop of frequent COPD guideline updates and heavy workloads in primary care, criteria for the appropriate use of ICS in COPD patients have not been effectively disseminated and implemented. Furthermore, compared with specialists, primary care physicians may have comparatively limited COPD-specific expertise, making them more inclined to adopt aggressive regimens to ensure symptom control and meet treatment expectations.[36,39,40]

Prescribing may also be shaped by clinical factors beyond guideline algorithms. Prior studies suggest that the inappropriate use of LABA/ICS and LABA/LAMA/ICS in group A and B patients is associated with the severity of airflow limitation, despite GOLD no longer using spirometric grade to direct pharmacotherapy.[40] In our cohort, however, only 14.6% of group A patients were GOLD stages 3–4, which does not fully account for the high rates of overuse of ICS-containing regimens. One study suggested that pulmonologists' choice for escalating or de-escalating COPD medication may depend on patients' symptoms (CAT score), response to previous treatment or exacerbations.[40] However, in this cohort, we further observed that, within Groups A, B, and E, the proportions of patients reporting respiratory symptoms, as well as CAT and SGRQ scores, did not differ meaningfully across guideline-adherent, inhaled medication underuse, and inhaled medication overuse subgroups. Although the small number of guideline-adherent cases in groups A and B likely limits statistical power, this may suggest that the use of higher-level inhaled therapy was generally not associated with patients' symptom reporting, CAT score or SGRQ score. This is different with findings from specialist-based studies, in which higher adherence to the GOLD strategy has been associated with greater symptom burden, as reflected by higher mMRC and CAT scores, highlighting potential differences in prescribing drivers between primary care and specialist settings.[35]

Additionally, disparities in access to different inhaled medications in China may drive nonadherence. A survey indicated that in primary care facilities, SABA is the most widely available inhaled medicine class (61.85%), LABA/ICS is stocked in roughly one-third of institutions, whereas LABA/LAMA and LABA/LAMA/ICS are available in only 7.69% and 7.38%, respectively.[41] These patterns likely reflect policy lag: LABA/ICS entered the National Essential Medicines List (NEML) in 2019,[42] whereas LABA/LAMA and LABA/LAMA/ICS were not added until 2022.[43] Such temporal gaps may have constrained the availability of certain drugs in primary care and led to earlier prescribing habits favoring LABA/ICS. Although our study was conducted in 2023, lingering use patterns may also reflect slower knowledge translation among primary care providers.

This study has several limitations. First, the cohort was assembled through non-random sampling, which may limit representativeness. Second, although guideline adherence was assessed against the initial treatment recommendations in GOLD, we did not distinguish between initiation and follow-up prescriptions; consequently, the results do not fully capture true guideline adherence. Third, our definitions of inhaled medication underuse and overuse reflect deviations from GOLD recommended prescribing patterns, and do not necessarily indicate clinical inappropriateness at the individual-patient level. No blood eosinophil count was available in this cohort, therefore the guideline adherence for group E participants may be overestimated. Nevertheless, the analysis still captures key aspects of real-world prescribing patterns. Finally, the cross-sectional design precludes longitudinal assessment of prescribing appropriateness; we were unable to evaluate how adherence evolved in response to changes in clinical status over time.

Future work should investigate determinants of guideline adherence of inhaled therapy prescriptions, elucidating the decision-making processes that lead to concordant versus non-concordant prescribing in COPD patients. Such insights can inform targeted interventions to improve patients' and physicians' awareness and knowledge about COPD, and standardize and improve COPD management in primary care settings.

Conclusion

In this primary care-based population of COPD patients with a recent history of exacerbations, the treatment patterns were dominated by LABA/ICS and LABA/LAMA/ICS, with overall low adherence to GOLD strategy recommendations, which was particularly pronounced in groups A and B, where inhaled medication overuse was common. It is necessary to improve prescription guideline adherence in the future to facilitate the implementation of standardized COPD management.

Abbreviations

BMI, body mass index; CAT, COPD Assessment Test; COPD, Chronic Obstructive Pulmonary Disease; GOLD, Global Strategy for Prevention, Diagnosis and Management of COPD; ICS, inhaled corticosteroids; LABA, long-acting beta agonists; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council; SABA, short-acting beta agonists; SAMA, short-acting muscarinic antagonist; SGRQ, St George's Respiratory Questionnaire.

Data Sharing Statement

The data are available from the last corresponding author, Professor Chunhua Chi, for proposals on reasonable requests that comply with national and institutional regulations for data sharing and collaborative research.

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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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