CLINICAL TRIAL REPORT

Current Status of the Treatment of COPD in China: A Multicenter Prospective Observational Study

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Background: There is a large gap in the treatments for patients with COPD according to the Global Initiative for COPD (GOLD) recommendations. Determining the situation of therapies in the real world is necessary. This study aimed to characterize the real-world practical therapies of COPD and prognosis of patients after treatment for 1 year.

Methods: This study was a multicenter prospective observational study performed using a database set up by the Second Xiangya Hospital of Center South University. Detailed usage information for pharmacotherapies and nonpharmacotherapies for patients was collected, as well as the consistency of recommendations and patient adherence. Moreover, the effect of therapies after 1 year was calculated by comparing lung function and symptoms.

Results: Ultimately, 4,796 patients with COPD from 12 hospitals in China were eligible. LAMA (39.1%), LAMA + LABA/ICS (39.0%) and LABA/ICS (14.4%) were the top three inhalants. We found that 42.7% of Group A patients, 61.6% of Group B patients and 30% of Group C patients were following inappropriate therapy, especially overuse of ICS. Only 3.9% (95% CI 2.4, 5.4) of patients used oxygen therapy, and 1.8% (95% CI 1.5, 2.3) used noninvasive positive pressure ventilation at home. Among these patients, 33.2% had poor adherence. A total of 452 patients completed 1 year of follow-up. After 1 year of treatment, the lung function of FEV_1/FVC decreased (P=0.001) and the mMRC score increased (P<0.001). There was no change in CAT scores (P>0.05).

Conclusion: This study highlights a significant discrepancy between recommendations for managing patients with COPD in GOLD report, and in real-world clinical practice in China. Over-prescription of ICS and under-prescription of nonpharmacologic therapy were common. The adherence to treatment of patients was poor, and the real-life treatment effectiveness was unsatisfactory. More attention should be paid to the implementation of recommendations and standardized administration of therapies.

Keywords: COPD, treatment, discrepancy, observational study

Plain Language Summary

Recommendations developed by Global Initiative for chronic obstructive pulmonary disease (COPD) (GOLD) are updated regularly. It is a reference for clinic physicians to treat patients with COPD all over the world. The compliance of the recommendations in clinic work is differentiated in different countries. We had collected the data of treatments for patients with COPD from 12 hospitals to observe current situation of therapies for COPD, and to investigate the gap between GOLD report and clinical practice in China. We had found that a high rate of discrepancy (40.5%) between GOLD 2017 recommendations and real-world clinical practice existed in China. Over-prescription of ICS (38.6%–55.6%) and under-

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prescription of nonpharmacologic therapy (0.08%–3.9%) were common. In addition, many researches have reported that kinds of inhalations for patients with COPD can improve the health quality, reduce the exacerbation rate and hospitalization rate. How about the therapeutic effect in the real world? If the inhaled treatments are really effective in the real world? The answer is in our study. We found that the adherence of medicines in patients with COPD was not very good (66.8%) and the real-life treatment effectiveness after 1 year of follow-up was unsatisfactory. We had listed some reasons about this phenomenon, such as the natural progress of disease and inappropriate therapy. Therefore, we recommended that more attention should be paid to the implementation of recommendations and standardized administration of therapies, including pharmacologic and nonpharmacologic treatments.

Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease with a prevalence of 13.7% in China that contributes to a large economic and social burden.[1,2] Inhaled bronchodilators are the first-line maintenance therapy for patients with COPD to reduce exacerbations and to improve quality of life and lung function.[3] The 2017 report developed by the updated Global Initiative for COPD (GOLD) recommends a proposed model for the initiation and subsequent escalation of pharmacologic management of stable COPD, according to the assessment of symptoms and exacerbation risk.[1] Although the GOLD recommendations have declared detailed therapies for patients with COPD, a significant dissociation has been reported between recommendations and clinicians' practices.[4,5] Nearly 62.1% of the treatments for patients with COPD are inappropriate, especially overprescription.[6] Among the COPD patients treated with triple inhaled therapy, 34.5% of the patients were classified as having mild disease (GOLD 1) and 40.8% as having moderate disease (GOLD 2).[7] The use of different inhaled drugs is markedly variable in different countries, similar to compliance with the COPD treatment recommendations.[8,9] Oral pharmacologic treatment can also be used as maintenance medication for patients with COPD. A few years ago, a multicenter study including 2,072 patients with COPD showed that theophylline (53.7%, 351/653) was the most commonly used treatment, followed by bronchodilators in China.[10]

There is a large gap in the treatments for patients with COPD according to the GOLD recommendations. This study aimed to observe the current status of treatments including pharmacotherapy and nonpharmacotherapy for stable COPD patients in China and to investigate the discrepancies between GOLD recommendations and real-world clinical practice. In addition, adherence to medicines in patients and effectiveness of treatments 1 year later were calculated.

Methods
Study Design and Data Source

This study was a prospective observational study performed in the real world from December 1, 2016 to October 31, 2019 using the database set up by the Second Xiangya Hospital of Center South University (ChiCTR-POC-17010431). We gathered data from 12 hospitals (10 hospitals in Hunan Province and 2 in Guangxi Province) in China (Website: http://218.4.234.74:9007/a/login). The study was approved by an institutional review board from the Second Xiangya Hospital of Central South University (2016076) and conducted in accordance with the Declaration of Helsinki. All data were compliant with Health Insurance Portability and Accountability Act to protect patient privacy. All participants provided written informed consent.

Patients

Patients were eligible for this study if they had a diagnosis of emphysema (identified by the International Classification of Diseases, Clinical Modification Tenth Revision [ICD-10] codes for emphysema: XJ43.xx) with the forced expiratory volume in 1 second (FEV_1)/forced volume vital capacity (FVC) ratio <0.7 or COPD (ICD-10 codes for COPD: XJ44.0, 44.8, 44.9) from the medical record.[11] Patients were at least 40 years of age and visited a pneumological outpatient clinic for the first time. Among these patients who had finished at least 1 year of follow-up were enrolled in our study to calculate the therapeutic effect. Patients with at least one medical claim with a diagnosis of asthma (ICD-10: XJ45.xx), bronchiectasis (ICD-10: XJ47), or lung cancer (ICD-10: C34.xx) during the study period were excluded.[11]

Basic Variables

Basic variables, including demographics, diagnosis, exacerbation history, lung function test, modified Medical Research Council (mMRC) score, COPD Assessment Test (CAT) score, and current therapy, were extracted from a disease-specific questionnaire (available as supplementary materials). Three technical assistants

reconfirmed all of the data to eliminate typing omission and errors. Smoking history was recorded in the study. Participants who had never smoked a cigarette or smoked less than 100 cigarettes in their life were defined as "Never smoker". Participants who had smoked ≥100 cigarettes in their life and currently smoked cigarettes were defined as "Current smoker". Participants who had smoked ≥100 cigarettes in their life but did not currently smoke and had quit smoking longer than 6 months, were defined as "Former smoker". At the follow-up visit, smoking cessation was considered equal to or longer than 6 months of abstinence.[12]

Pulmonary function was measured using a MasterScreen™ pulmonary function test system spirometer (Germany), and spirometric measurements met the standards of the American Thoracic Society and the European Respiratory Society.[13] According to the airway limitation severity of FEV_1, patients were divided into GOLD 1: FEV_1 >80% predicted, GOLD 2: 50% ≤ FEV_1 <80% predicted, GOLD 3: 30% ≤ FEV_1<50% predicted, and GOLD 4: FEV_1<30% predicted.

Exacerbations were defined as an acute worsening of respiratory symptoms that results in additional therapy.[14] Exacerbations can be classified into three levels: mild (treated with short-acting bronchodilators only, SABDs), moderate (treated with SABDs plus antibiotics and/or oral corticosteroids) and severe (patient requires hospitalization or visits the emergency room). In our research, patient estimates of moderate and severe exacerbation numbers in the past year before they visited were recorded.[15] According to the history of exacerbations and severity of symptoms by the CAT and mMRC questionnaires, patients were classified into Groups A/B/C/D.[1]

Treatments

Detailed treatments, including pharmacotherapy (inhaled and oral) and nonpharmacotherapy, were extracted from the study. Inhaled COPD treatment was recorded at the moment of every visit. All COPD treatments were classified as short-acting bronchodilators (SABDs): short-acting β2-agonists (SABAs) and short-acting muscarinic agonists (SAMAs); long-acting bronchodilators (LABDs): long-acting β2-agonists (LABAs) and long-acting muscarinic agonists (LAMAs); and other inhalations: LAMA combined with LABA (LAMA/LABA) in an inhaler, LABA combined with inhaled corticosteroid (LABA/ICS) in an inhaler and ICS monotherapy. Oral therapy with theophylline was recorded. In addition,

nonpharmacologic therapies such as home oxygen therapy, noninvasive positive pressure ventilation (NIPPV) at home, vaccination, pulmonary rehabilitation and lung transplantation were calculated in our study. In this study, LABA/ICS means that LABA and ICS were administered in an inhaler. LAMA/LABA also means they are in an inhaler. "+" means "and", which was defined to indicate inhalations with different inhalers used simultaneously by patients.

Consistency with GOLD Recommendations

On the basis of GOLD 2017, the appropriateness of the inhaled pharmacological treatment of COPD patients was established for Groups A/B/C/D.[1] The first choice of inhaled therapy for different groups is recommended as follows, if not defined as inappropriate therapy or as a discrepancy with the GOLD report.

Group A: A short- or a long-acting bronchodilator.
Group B: LAMA or LABA, or LAMA + LABA.
Group C: LAMA, or LABA + ICS or LAMA + LABA.
Group D: LAMA, or LAMA + LABA or LABA + ICS, or LAMA + LABA+ICS.

Patient Adherence

During the 1-year of follow-up, telephone contact follow-ups were arranged every 6 months following the first visit at the outpatient clinic through a follow-up questionnaire, including numbers of exacerbations, smoking history, changes in therapies and reasons for drug withdrawal (available as supplementary materials). Patients were considered fully adherent if they reported having taken their medication every day within the last 30 days; otherwise, they were recording as having poor adherence.[16] The reasons for poor adherence were recorded, including feeling better and not needing to continue treatments, ineffective, worried about adverse effects of drugs, cumbersome inhalation techniques, economic burden and other reasons such as accessibility of drugs.

Effect of Therapy

Patients with COPD who had been followed for at least 1 year were enrolled. The demographic data, pharmacotherapy, exacerbations, lung function, CAT and mMRC were recorded. Changes in lung function and symptoms (CAT and mMRC scores) were used to calculate the effect of therapy.

Statistical Analysis

Descriptive statistics included the absolute and relative frequencies for categorical variables and the mean ± SD for numerical variables. Continuous variables were statistically compared using t-tests, and categorical variables were compared using the nonparametric test. To test for differences in proportion in some variables according to the type of bronchodilators taken, a Chi-square test or Fisher's test was used. We considered a p-value less than 5% as statistically significant. We used the approximate normal distribution method to compute binomial proportion 95 confidence intervals. When we calculated the pharmacotherapy in different groups and grades, and effect of therapy in the follow-up, we had removed some missing data to avoid data bias. All analyses were performed using PASW version 18.0 software (PASW, Inc., Chicago, Illinois).

Results

Patient Selection and Demographics

In total, data from 8,058 patients with COPD were enrolled in our study. Among these patients, 4,796 (59.5%) met the inclusion criteria. In this population, 452 patients with COPD who finished 1 year of follow-up were recorded (Figure 1). The demographic characteristics of all the patients with COPD are shown in Table 1. The mean age was 64 years and the majority were male (87.7%). A total of 41.5% of the patients were current smokers. The mean of FEV_1% predicted and the FEV_1/FVC% were 47.6% and 48.6%, respectively. The mean CAT score was 16.3. Patients were assigned to Groups A (8.0%), B (55.5%), C (1.5%), and D (35.0%). The classifications were as follows: GOLD 1 (7.6%), 2 (33.9%), 3 (37.9%) and 4 (20.6%).

Pharmacotherapy

The treatment therapies are shown in Table 2. LAMA (39.1%), LAMA + LABA/ICS (39.0%) and LABA/ICS (14.4%) were the top three inhalants used. It is worth mentioning that for 11.4% (545/4796) of patients, theophylline was also used.

The detailed pharmacotherapies of 4,001 COPD patients in Groups A/B/C/D are shown in Table 3. A total of 795 patients were excluded because of incomplete data. In Group A, LAMA (55.5%) was commonly used. We found that 42.7% (137/321) of Group A patients were following inappropriate therapy. In Group B, LAMA + LABA/ICS was also the most common (39.9%). A total of 61.6% (1367/2219) were following a therapy in contrast with

GOLD recommendations. Among Group C patients, 53.3% were using LAMA, while 30% (18/60) were following an inappropriate therapy. In Group D, LAMA + LABA/ICS was also the most prescribed (44.3%). Only 6.9% (97/1401) were following an inappropriate therapy. The overall discrepancy rate between GOLD recommendations and clinical practice was 40.5% (1619/4001) in Groups A/B/C/D. LAMA/LABA was only used in Groups B (0.2%) and D (0.1%). ICS overtreatment occurred in 55.6% (1413/2540) of patients in Groups A and B. Among the different groups, significant differences were found in the proportions of LAMA, LABA/ICS and LAMA + LABA/ICS ($P<0.001$, $P=0.004$ and $P<0.001$, respectively).

The pharmacotherapies of 3,820 COPD patients in GOLD 1/2/3/4 grades are presented in Table 4. A total of 976 patients were removed because of a lack of lung function tests. We found that there were significant differences across the LAMA, LABA/ICS and LAMA + LABA/ICS treatments ($P<0.001$, $P=0.044$ and $P<0.001$). When compared to other grades, LAMA was used less as the grade increased, with 70.2% in GOLD 1, 51.9% in GOLD 2, 31.0% in GOLD 3 and 20.0% in GOLD 4. In contrast, LAMA + LABA/ICS was commonly used in GOLD 4 (60.7%), followed by GOLD 3 (47.3%), GOLD 2 (23.1%) and GOLD 1 (6.8%). ICS was overused in 38.6% (612/1587) of cases in GOLD 1/2. When treatments were based on symptoms or airway limitation, there were some inappropriate treatments with SABDs combined with ICS or LABDs (5.6% and 5.6%, respectively).

Nonpharmacologic Therapy

In this population, nonpharmacologic therapies were used, including 3.9% (95% CI 2.4, 5.4) home oxygen therapy, 1.8% (95% CI 1.5, 2.3) NIPPV at home, 0.3% (95% CI 0.01,1.2) vaccination, 0.1% (95% CI 0.0, 5.6) pulmonary rehabilitation, and 0.08% (95% CI 0.0, 0.2) lung transplantation. Among the patients, 33.2% had poor adherence after 6 months of follow-up. When the COPD patients were asked about the reasons for withdrawal, 30.0% of them thought that they were better and did not need to continue treatments, 18.5% considered the treatment ineffective, 14.5% had trouble with inaccessibility of drugs, 1.9% worried about adverse effects, and 0.7% considered the economic burden, while, 34.4% gave other reasons.

Effect of Therapy

The baseline clinical characteristics of 452 COPD patients treated for at least 1 year are presented in Table 5. The
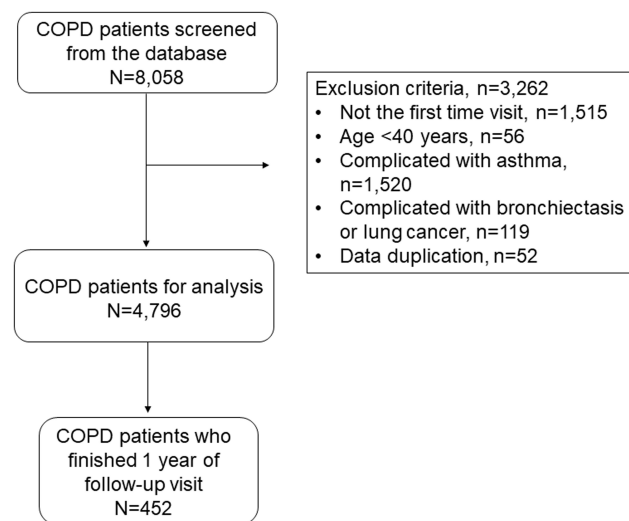
Figure 1 Patient selection flowchart. In total, data from 8,058 patients with COPD were collected in our study. Among these patients, 4,796 (59.5%) met the inclusion criteria of diagnosis of COPD. There were 3,262 (40.5%) patients excluded, including 1,515 patients were not the first time at the outpatient clinic, 56 were younger than 40 years old, 1520 of co-existing asthma, 119 with bronchiectasis and lung cancer, and 52 data duplicated. In this population, there were 452 of patients with COPD who finished at least 1 year of follow-up.
Note: Data were extracted on October 31, 2019.

changes in patients after treatment are shown in Table 6. The numbers of moderate and severe exacerbations were obviously increased (1 vs 2, and 0 vs 2, $P<0.001$ and $P<0.001$, respectively). The lung function of FEV_1/FVC decreased ($P=0.001$), and the mMRC score increased ($P<0.001$). There was no change in FEV_1 and CAT scores ($P=0.732$ and $P=0.094$, respectively). One year later, the poor adherence rate of treatment was 20.4% (79/387). The use of LAMA declined ($P <0.001$), while the use of LAMA + LABA/ICS increased ($P=0.009$).

Discussion

This real-world prospective observational study demonstrated that the treatment modalities for patients with COPD had major discrepancies compared to GOLD 2017 report, especially overuse of LABA/ICS and LAMA + LABA/ICS. The use of nonpharmacologic therapy including home oxygen therapy, NIPPV, vaccine, pulmonary rehabilitation and lung transplantation, was seriously insufficient in China. Poor adherence to treatment in patients and unsatisfactory therapeutic effect after 1 year of follow-up were identified.

In our study, the majority of COPD patients were divided into Groups B/D and GOLD 2/3 grades. LAMA, LAMA + LABA/ICS and LABA/ICS inhalants were commonly used to treat these patients. Except for Group D, there was a high rate of inconsistency with the GOLD

recommendations in Groups A/B/C (42.7% in Group A, 61.6% in Group B, and 30% in Group C). This was consistent with Grewe FA's study.[17] They also found that prescriptions in patients with very severe COPD were most likely to comply with recommendations. LAMA was the most frequently used treatment in Group A according to our study, which is inconsistent with a study in the UK primary care setting.[8] In their population, LABA + ICS therapies were the most commonly used. Overtreatment of ICS combined with one or more long-acting bronchodilators was demonstrated as the most common inappropriate prescription in patients with COPD, whether categorized by symptom or airway limitation, and was lower than in other studies.[18] One reason for the overuse may be the lack of inhalation formulations of LABA and LAMA/LABA available on the market until 2019 in China. The longer marketing history and better availability of LAMA and LABA/ICS in the public health care system may contribute to their much higher utilization rate. When classified based on airflow limitation, we found that the use of LAMA was lower as the grades increased, which was inverse in triple therapies. Before the GOLD 2017 was issued, many physicians treated COPD patients according to the severity of airway limitation,[19] and the influence can be seen currently.

Oral pharmacologic treatment with theophylline is still commonly used in China, although it has been relegated to third-line therapy in the current GOLD recommendations. Ram et al[20] found that theophylline has a modest effect on lung function in moderate to severe COPD. Compared with other inhaled bronchodilators, theophylline was much less expensive and its prescription was not restricted by the public health care system in China. Devereux et al[21] showed that in people with COPD at high risk of exacerbation, no benefit came from the addition of low-dose theophylline. Studies of the real function of theophylline in patients with different severities of COPD are warranted in the future.

We also investigated the current status of nonpharmacologic treatment. For example, home oxygen therapy, which can improve survival in patients with COPD, was rarely used (3.9%) in this study. In other countries, home oxygen therapy appears to be universal in patients with COPD.[22,23] Home NIPPV has been determined to improve outcomes in COPD patients with chronic respiratory failure. It was used at home in only 1.8% of our population because its use was only considered in some selected patients with pronounced daytime hypercapnia.[24] Vaccination is recommended for the management of

Table 1 Baseline Clinical Characteristics of COPD Patients (N=4796)

Baseline Clinical Characteristics	COPD Patients	Missing Data
Age (years), mean ± SD	64.5±8.9	0 (0)
Male, n (%)	4205 (87.7)	0 (0)
BMI, mean ± SD	22.3±3.6	1074 (22.4)
Educational level, n (%)		635 (13.2)
Primary school or below	1820 (43.7)	
Middle school	1571 (37.8)	
High school	586 (14.1)	
College or above	184 (4.4)	
Marital status, n (%)		548 (11.4)
Unmarried	35 (0.8)	
Married	4078 (96.0)	
Divorce	14 (0.3)	
Widowhood	121 (2.8)	
Smoking history, n (%)		710 (14.8)
Never smoker	781 (19.1)	
Current smoker	1697 (41.5)	
Former smoker	1608 (39.4)	
Lung function, mean ± SD		976 (20.4)
FEV_1, % predicted	47.6±20.2	
FEV_1/FVC%	48.6±12.7	
CAT, mean ± SD	16.3±6.3	586 (12.2)
<10	601 (14.3)	
10–20	2406 (57.1)	
≥20	1203 (28.6)	
mMRC, median (IQR)	2 (1, 3)	586 (12.2)
0 or 1	1326 (31.5)	
≥2	2884 (68.5)	
Exacerbation history, median (IQR)	1 (0, 2)	771 (16.0)
Moderate	0 (0, 1)	
Severe	0 (0, 1)	
GOLD stages, n (%)		795 (16.6)
A	321 (8.0)	
B	2219 (55.5)	
C	60 (1.5)	
D	1401 (35.0)	
GOLD Classifications, n (%)		976 (20.4)
GOLD 1	292 (7.6)	
GOLD 2	1295 (33.9)	
GOLD 3	1447 (37.9)	
GOLD 4	786 (20.6)	

Note: Mean ± SD for numerical variables, median (IQR) for categorical variables.
Abbreviations: FEV_1, forced expiratory volume in 1 second; FEV1/FVC, FEV_1 to forced vital capacity; CAT, COPD Assessment Test; mMRC, modified Medical Research Council Dyspnea Scale.

Table 2 Description of Inhalation Therapies Used in the Study Population (N=4796)

Therapies, Only Used, n (%)	COPD Patients
Monotherapy	
SABA	23 (0.5)
SAMA	20 (0.4)
LABA	1 (0.02)
LAMA	1875 (39.1)
ICS	9 (0.2)
Dual therapy	
LABA/ICS	689 (14.4)
LAMA+ICS	7 (0.1)
LAMA/LABA	5 (0.1)
Triple therapy	
LAMA+LABA/ICS	1872 (39.0)
Other therapies	
LABA/ICS+ICS	1 (0.02)
LABA/ICS+LAMA/LABA	1 (0.02)
SABA+SAMA	1 (0.02)
SABA+ICS	1 (0.02)
SABA or SAMA+LABA/ICS	47 (1.0)
SABA or SAMA+LAMA	83 (1.7)
SAMA+LABA/LAMA	3 (0.06)
SABA or SAMA+LAMA+LABA/ICS	123 (2.6)
SABA+SAMA+ LABA/ICS	1 (0.02)
SABA+SAMA+LAMA+LABA/ICS	3 (0.06)
SAMA +LAMA+LABA/ICS+ICS	1 (0.02)

Notes: LABA/ICS means LABA and ICS are in an inhaler. LAMA/LABA also means they are in an inhaler. "+" means "and", it was defined to show the all inhalations with different inhalers used simultaneously by patients.
Abbreviations: SABA, short-acting β2-agonist; SAMA, short-acting muscarinic agonist; LAMA, long-acting muscarinic antagonist; LABA, long-acting β2-agonist; ICS, inhaled corticosteroids; NIPPV, non-invasive positive pressure ventilation.

COPD patients, especially those over 50 years of age.[25] However, it was rarely used (0.3%) in this study, with considerably lower rates than in the United States population, which has a vaccination rate of 48.5%.[26] We need to pay more attention to the implementation of vaccines and the awareness of patients and physicians.[27] Moreover, few COPD patients (0.1%) participated in pulmonary rehabilitation in our study, which was lower than that in some developed countries. In Canada, 0.4% of all Canadians with COPD have access to pulmonary rehabilitation, and in Australia, 5–10% of the patients with moderate to severe COPD have access.[28,29] Factors including insufficient knowledge, attitudes for physicians and perceived practical/physical concerns for patients are related to influence patients' participation.[30,31] Interventional therapy of lung transplantation was also scarce in our study. It is an

Table 3 Description of Inhalation Therapies Used in Different GOLD-Groups (N=4001)

Therapies, Only Used, n (%)	Group A (n=321)	Group B (n=2219)	Group C (n=60)	Group D (n=1401)	P value
Mono inhaled therapy					
SABA	5 (1.6)	7 (0.3)	0 (0)	4 (0.3)	N/A
LABA	0 (0)	0 (0)	0 (0)	1 (0.1)	N/A
SAMA	1 (0.3)	10 (0.4)	0 (0)	4 (0.3)	N/A
LAMA	178 (55.5)	848 (38.2)	32 (53.3)	531 (37.9)	<0.001*
ICS	0 (0)	3 (0.1)	0 (0)	4 (0.3)	N/A
Dual inhaled therapy					
LABA/ICS	56 (17.4)	305 (13.7)	10 (16.7)	151 (10.8)	0.004*
LAMA+ICS	1 (0.3)	4 (0.2)	0 (0)	1 (0.1)	N/A
LABA+LAMA	0 (0)	4 (0.2)	0 (0)	1 (0.1)	N/A
Triple inhaled therapy					
LAMA+LABA/ICS	60 (18.7)	886 (39.9)	17 (28.3)	621 (44.3)	<0.001*
Other inhaled therapies					
SABA+LABA/ICS	6 (1.9)	18 (0.8)	1 (1.7)	7 (0.5)	N/A
SABA or SAMA +LAMA+LABA/ICS	2 (0.6)	60 (2.7)	0 (0)	46 (3.3)	N/A
SABA+LAMA	2 (0.6)	27 (1.2)	0 (0)	15 (1.1)	N/A
SAMA+LAMA	6 (1.9)	15 (0.7)	0 (0)	3 (0.2)	N/A
SAMA+LAMA/LABA	0 (0)	2 (0.1)	0 (0)	1 (0.1)	N/A
SAMA+LABA/ICS	0 (0)	8 (0.4)	0 (0)	2 (0.1)	N/A
SABA+ICS	0 (0)	1 (0.04)	0 (0)	0 (0)	N/A
LABA/ICS+ICS	0 (0)	1 (0.04)	0 (0)	0 (0)	N/A
SABA+SAMA+LAMA+LABA/ICS	0 (0)	1 (0.04)	0 (0)	2 (0.1)	N/A
SAMA+LAMA+LABA/ICS+ICS	0 (0)	1 (0.04)	0 (0)	0 (0)	N/A

Notes: LABA/ICS means LABA and ICS are in an inhaler. LAMA/LABA also means they are in an inhaler. "+" means "and", it was defined to show the all inhalations with different inhalers used simultaneously by patients. To test for differences of proportion in some variables according to the type of bronchodilators taken, a Chi-square test was used, *$P<0.05$. N/A means not applicable.
Abbreviations: SABA, short-acting β2-agonist; SAMA, short-acting muscarinic agonist; LAMA, long-acting muscarinic antagonist; LABA, long-acting β2-agonist; ICS, inhaled corticosteroids.

alternative treatment modality for patients with end-stage COPD. Further study is still required to assess the overall survival benefit of lung transplantation in the COPD patient population.[32]

Nonadherence to treatments in patients with COPD is common all over the world. In our study, a total of 33.2% of the patients stopped medication after 6 months of follow-up. In the USA, the proportion of patients with non-adherence to triple therapy at 6 months was 59.0% in a commercially insured population.[33] Tøttenborg et al[34] showed that a higher risk of poor adherence was present among unemployed and low-income patients. However, we found that patients feeling better and seeing no need to be treated, considering the treatment ineffective and encountering access restrictions contributed to poor adherence. Unwillingness and privacy issues may be the two main reasons why patients avoid their economic problems in China.

Many studies have shown that dual or triple therapy will produce a statistically significant improvement in FEV_1 and reduce the exacerbation risk compared among different groups.[35–37] Unfortunately, in our study, the lung function of FEV_1/FVC, symptoms of dyspnea and exacerbations after 1-year of follow-up were not improved, even worse compared to the baseline. The FEV_1 and CAT scores were stable. In other words, the treatment resulted in little improvement in symptoms and lung function over time. One reason for this phenomenon is that lung function will decline nearly 53 mL per year for COPD patients.[38] In addition, inhaler misuse has been associated with poor disease control, which is common in not only naive but also experienced users. Schedule education and proper evaluation of inhalation, such as the FSI-10 questionnaire, are important for teaching patients with COPD how to handle the inhaler.[39] Moreover, the inappropriate therapies and poor adherence to treatment were the main contributors to poor therapeutic effect in this study.

Table 4 Description of Inhalation Therapies Used in Different GOLD Classifications Based on Airflow Limitation (N=3820)

Therapies, Only Used, n (%)	GOLD 1 (n=292)	GOLD 2 (n=1295)	GOLD 3 (n=1447)	GOLD 4 (n=786)	P value
Monotherapy					
SABA	2 (0.7)	14 (1.1)	1 (0.1)	5 (0.6)	N/A
LABA	0 (0)	0 (0)	1 (0.1)	0 (0)	N/A
SAMA	9 (3.1)	3 (0.2)	2 (0.1)	2 (0.3)	N/A
LAMA	205 (70.2)	672 (51.9)	448 (31.0)	157 (20.0)	<0.001*
ICS	0 (0)	1 (0.1)	1 (0.1)	5 (0.6)	N/A
Dual therapy					
LABA/ICS	36 (12.3)	207 (16.0)	221 (15.3)	94 (12.0)	0.044*
LAMA+ICS	0 (0)	2 (0.2)	0 (0)	0 (0)	N/A
LABA/LAMA	0 (0)	3 (0.2)	2 (0.1)	0 (0)	N/A
Triple therapy					
LAMA+LABA/ICS	20 (6.8)	299 (23.1)	684 (47.3)	477 (60.7)	<0.001*
Other therapies					
SABA+LABA/ICS	2 (0.7)	14 (1.1)	0 (0)	5 (0.6)	N/A
SABA or SAMA +LAMA+LABA/ICS	0 (0)	23 (1.8)	50 (3.5)	29 (3.7)	N/A
SABA+SAMA	0 (0)	0 (0)	1 (0.1)	0 (0)	N/A
SABA+LAMA	3 (1.0)	23 (1.8)	13 (0.9)	5 (0.6)	N/A
SAMA+LAMA	10 (3.4)	11 (0.8)	3 (0.2)	0 (0)	N/A
SAMA+LAMA/LABA	0 (0)	1 (0.1)	2 (0.1)	0 (0)	N/A
SAMA+LABA/ICS	0 (0)	8 (0.6)	10 (0.7)	1 (0.1)	N/A
SABA+ICS	0 (0)	0 (0)	1 (0.1)	0 (0)	N/A
LABA/ICS+ICS	0 (0)	0 (0)	1 (0.1)	0 (0)	N/A
SAMA+LAMA+LABA/ICS+ ICS	0 (0)	0 (0)	0 (0)	1 (0.1)	N/A

Notes: LABA/ICS means LABA and ICS are in an inhaler. LAMA/LABA also means they are in an inhaler. "+" means "and", it was defined to show the all inhalations with different inhalers used simultaneously by patients. To test for differences of proportion in some variables according to the type of bronchodilators taken, a Chi-square test was used, *P<0.05. N/A means not applicable.
Abbreviations: GOLD, Global Initiative for COPD; SABA, short-acting β2-agonist; SAMA, short-acting muscarinic agonist; LAMA, long-acting muscarinic antagonist; LABA, long-acting β2-agonist; ICS, inhaled corticosteroids.

The present study is subject to several limitations. First, there were missing data in our study. No significant difference in treatments was found compared to the available data group. Moreover, we used statistical methods such as deleting the missing data at random and mean completers to reduce the bias. Therefore, we thought the outcomes were not affected by missing data. Second, our study is a multicenter prospective observational study in the real world at the outpatient clinic to investigate the current status of treatments for patients with COPD. LABA/LAMA was not accessible in each hospital until 2019, which led to a low usage rate. Third, only a few of COPD patients were followed for 1 year. That was because we did not take intrusive measures to improve the rate of follow-up visits in order to restore the real condition in China. In our country, the Universal Health Care will not cover the cost patients have at the outpatient clinic. Most of the patients in our study came from remote rural areas and reluctant to revisit the same hospitals due to transportation costs and medical expenses. Therefore, patients can choose to visit any hospital or doctor they want, which possibly leads to the missing follow-ups in our research centers. Perhaps more studies should be conducted to investigate the prognosis and mortality of patients who are lost to follow-up in the future.

Conclusions

In summary, the findings of this study provide insights into current status of treatment in patients with COPD in the real world in China. There was a high rate of discrepancy between the GOLD recommendation and the real-world clinical practice. Over-prescription of ICS and under-prescription of non-pharmacologic therapy were common. The adherence of treatment in patients is not good, and the real effects of treatment are still unsatisfactory. Our results suggest that more attention should be paid to the implementation of GOLD

Table 5 Baseline Clinical Characteristics of COPD Patients Finished 1 Year of Follow-Up Visit (N=452)

Baseline Clinical Characteristics	One Year of Follow-Up
Age (years), mean ± SD	61.2±7.9
Male, n (%)	432 (95.6)
BMI, mean ± SD	22.5±3.3
Educational level, n (%)	
Primary school or below	195 (43.1)
Middle school	179 (39.6)
High school	56 (12.4)
College or above	22 (4.9)
Marital status, n (%)	
Unmarried	5 (1.1)
Married	435 (96.2)
Divorce	4 (0.9)
Widowhood	8 (1.8)
Smoking history	
Never smoker	81 (18.0)
Former smoker	229 (50.7)
Current smoker	141 (31.3)
Lung function, mean ± SD	
FEV_1, % predicted	47.3±19.4
$FEV_1/FVC\%$	49.6±12.0
CAT, mean ± SD	15.0±6.2
mMRC, median (IQR)	2 (1, 3)

Note: Mean ± SD for numerical variables, median (IQR) for categorical variables.
Abbreviations: COPD, chronic obstructive pulmonary disease; BMI, body mass index; GOLD, Global Initiative for COPD; CAT, COPD Assessment Test; mMRC, modified Medical Research Council Dyspnea Scale.

recommendations and standardized administration of therapies, including inhaled bronchodilators, oral pharmacologic and nonpharmacologic treatments. Different kinds of bronchodilators should be marketed and accessible at different levels of hospitals and areas in China.

Abbreviations

COPD, chronic obstructive pulmonary disease; BMI, body mass index; GOLD, Global Initiative for COPD; CAT, COPD Assessment Test; mMRC, modified Medical Research Council Dyspnea Scale; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; SABA, short-acting β2-agonist; SAMA, short-acting muscarinic agonist; LAMA, long-acting muscarinic antagonist; LABA, long-acting β2-agonist; ICS, inhaled corticosteroids; SABDs, short-acting bronchodilators; LABDs, long-acting bronchodilators; NIPPV, non-invasive positive pressure ventilation.

Table 6 Lung Function, Symptoms and Inhalation Therapy at Baseline and After 12 Months (N=452)

Variates	COPD Patients		P value
	Baseline	Follow-Up	
Exacerbations, median (IQR)	n=420	n=452	
Moderate	1 (0, 2)	2 (2, 2)	<0.001*
Severe	0 (0, 0)	2 (1, 2)	<0.001*
Lung function, mean ± SD			
Pre-bronchodilator	n=358	n=358	
FEV_1, % predicted	48.0±19.3	47.7±19.0	0.732
$FEV_1/FVC\%$	50.0±11.9	48.7±12.0	0.001*
CAT, mean ± SD	n=427	n=427	
	15.0±6.2	14.5±6.7	0.094
mMRC, median (IQR)	n=427	n=427	
	2 (1, 3)	2 (2, 3)	<0.001*
Inhalants, total, n (%)	n=387	n=308	
Monotherapy			
SABA	0 (0)	0 (0)	N/A
LABA	0 (0)	0 (0)	N/A
SAMA	1 (0.3)	1 (0.3)	N/A
LAMA	187 (48.3)	108 (35.1)	<0.001*
ICS	0 (0)	0 (0)	N/A
Dual therapy			
LABA/ICS	49 (12.7)	45 (14.6)	0.455
LAMA+ICS	0 (0)	1 (0.3)	
LAMA/LABA	0 (0)	1(0.3)	
Triple therapy			
LAMA+LABA/ICS	138 (35.7)	140 (45.5)	0.009*
Other therapies			
SABA+LABA/ICS	2 (0.5)	1(0.3)	N/A
SABA+LAMA	2 (0.5)	2 (0.6)	N/A
SABA or SAMA +LAMA +LABA/ICS	8 (2.1)	7 (2.2)	0.889

Notes: LABA/ICS means LABA and ICS are in an inhaler. LAMA/LABA also means they are in an inhaler. "+" means "and", it was defined to show the all inhalations with different inhalers used simultaneously by patients; Continuous variables were statistically compared using paired *t*-test, categorical variables were compared using Wilcoxon matched-pairs signed-rank test; Chi-square test or Fisher's test was used to compare the proportion between the two groups, *$P<0.05$; N/A means not applicable.
Abbreviations: CAT, COPD Assessment Test; mMRC, modified Medical Research Council Dyspnea Scale; SABA, short-acting β2-agonist; SAMA, short-acting muscarinic agonist; LAMA, long-acting muscarinic antagonist; LABA, long-acting β2-agonist; ICS, inhaled corticosteroids.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available in the Department of Pulmonary and Critical Care Medicine, the Second Xiangya Hospital repository http://218.4.234.74:9007/a/

login. The data that support the findings of this study are available upon reasonable request from the author Yuqin Zeng or Pingchen.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; revised the article critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

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