REALizing and improving management of stable COPD in China: Results of a multicentre, prospective, observational study (REAL)

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Abstract

Background

Chronic obstructive pulmonary disease (COPD) management in China is far from adequate, with underdiagnosis and undertreatment being the major barriers to optimal care and improved patient outcomes. To better understand the burden of COPD and its management in China, real-world characterization of the severity and treatment of COPD across the country is needed.

Methods

We conducted a 52-week multicentre, prospective, observational study on outpatients (≥ 40 years old) diagnosed with COPD, enrolled from 50 secondary and tertiary hospitals across six geographical regions. Data were collected in routine clinical practice.

Results

Between December 2017 and August 2020, 5013 patients were enrolled and 4978 included in the analysis. Mean (standard deviation [SD]) age was 66.2 (8.9) years and 79.5% were male. Most COPD outpatients (90%) had moderate-to-very-severe airflow limitation (Global Initiative for Chronic Obstructive Lung Disease [GOLD] II–IV). Overall, the annual rate (per patient) of COPD exacerbations of any severity was 0.56 (95% confidence interval [CI]: 0.54–0.58). During 1-year, 1536 (30.8%) patients experienced ≥ 1 exacerbation of any severity and 960 (19.3%) patients had ≥ 1 exacerbation requiring hospitalization/emergency visit. The annual severe exacerbation rate was 0.31 (95% CI: 0.29–0.33). Mean (SD) COPD assessment test score was 14.6 (7.6) at baseline and 10.6 (6.8) at follow-up; however, 42–55% of patients had persistent dyspnoea, chest tightness and wheezing at 1-year. The most prescribed treatments were inhaled corticosteroid (ICS)/long-acting β2-agonist (LABA) combination (36.0%), ICS/LABA + long-acting muscarinic antagonist (LAMA) (17.7%) and LAMA monotherapy (15.3%). Among patients with high exacerbation risk (GOLD Groups C and D), 10.1% and 13.1, respectively, did not receive any long-acting inhalers; only 53.8% and 63.6% of Group C and D patients with ≥ 1 exacerbation during follow-up were prescribed ICS-containing therapy, respectively. Mean (SD) adherence (actual drug taken days/follow-up days) for long-acting inhalers was 59.0% (34.3). Mean (SD) score for the COPD questionnaire was 6.7 (2.4).

Conclusions

These results indicate a high burden of severe exacerbations and symptoms in Chinese outpatients with COPD, and low adherence with treatment guidelines, highlighting the need for more effective management nationwide.

Trial Registration:

The trial was registered on 20 March 2017 (ClinicalTrials.gov identifier: NCT03131362).

Background

Chronic obstructive pulmonary disease (COPD) is a rapidly rising global public health issue; COPD prevalence increased by 32% between 2015 and 2017, to an estimated 544.9 million adults worldwide [1–3]. In China, 8.6% of adults aged ≥ 20 years (99.9 million) and up to 13.7% of those aged ≥ 40 years are affected by COPD in 2018 [4]. According to the Global Burden of Disease Study, COPD was responsible for over 0.9 million deaths in China in 2013, making it is one of the leading causes of mortality in the country [5]. With increasing air pollution [6, 7], high rates of smoking [8], and an ageing population in China [9, 10], COPD burden and the associated mortality in China may increase further in the coming decades. Acute exacerbations are one of the major risk factors for increased mortality, as well as decline in lung function and quality of life in patients with COPD. Management of exacerbations places an enormous economic burden on both patients and healthcare systems. Importantly, the risks associated with COPD exacerbations are modifiable, suggesting the COPD burden may be improved by optimal evidence-based management [11].

Unfortunately, COPD management in China is far from adequate. The 2013 national guideline for diagnosis and management of COPD in China is currently not referred to in clinical practice [12–14]. Furthermore, pharmacological and non-pharmacological management of COPD in China does not adhere to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) evidence-based strategy document for the management of patients with COPD [13–17]. In addition to undertreatment, the underdiagnosis of patients with COPD is a major barrier to optimal care and improved patient outcomes [18]. Results from a nationwide survey conducted in China (N = 19,994) revealed that 16.6% of the adult population had a suspected risk of COPD but did not receive a diagnosis; of those with an identified risk, only 16.7% were aware of COPD [9]. Underdiagnosis can occur due to patients not recognizing early COPD symptoms, and as a result, underreporting them [19, 20]. A community-based survey (N = 25,011) conducted across 10 regions in China between 2013 and 2014 showed that 80% of patients with COPD had a limited understanding of their diagnosis, with poor levels of disease awareness more pronounced in rural than in urban areas (87% vs 73%) [14]. Understanding the disease characteristics (including symptoms, exacerbations, and disease severity), disease knowledge among patients, and current treatment patterns are important first steps in improving early detection and optimising management, which in turn are crucial in modifying the clinical course of COPD and improving patient outcomes.

The COPD status in China has previously been assessed in cross-sectional, short-term, or regional studies, in which key information such as exacerbation frequency, treatment patterns, symptoms, and costs may be missed [4, 5, 9, 14, 21]. Moreover, study duration and sample size may not be appropriate to examine exacerbation rates and cover seasonality. Data on COPD status in China also vary substantially between regional studies [4, 5, 9, 14], demonstrating they are likely to be unrepresentative of the

nationwide situation. Due to these shortcomings, there are currently many knowledge gaps regarding COPD status among outpatients in China. The REALizing and improving the management of stable COPD in China study was conducted to generate reliable information on COPD management, outcomes, treatment pattern and adherence, as well as disease knowledge among a large and nationally representative sample of COPD outpatients in China by assessing 1-year outcomes in a real-world setting.

Methods

Details on the study design and population have been published previously [22]. Briefly, REAL was a multicentre, prospective, observational study conducted at 50 secondary and tertiary hospitals across six geographic regions in China. A multistage stratified random sampling method was used to select a nationally representative sample of hospitals with respiratory departments.

Adult outpatients aged ≥ 40 years with a clinical diagnosis of COPD (as per GOLD 2016 criteria) were enrolled during routine visits. Patients who had participated in an interventional clinical trial in the 30 days prior to enrolment, and those with an acute exacerbation within the previous 4 weeks were excluded. No additional restrictions for inclusion or exclusion were used to ensure the study population was representative of real-world clinical practice. All eligible patients provided a written informed consent.

During the study, patients underwent clinical assessments and received medical care as per routine clinical practice and at the discretion of the treating physician.

Data collection

All eligible patients were prospectively followed for 12 months, or until study discontinuation, whichever occurred first. The study comprised two on-site visits (baseline and at study end) and three telephone follow-ups, which were scheduled every 3 months. Data on demographics, baseline characteristics, disease status, treatment and clinical outcomes were collected at baseline and at follow-up visits, as part of the routine clinical practice, using a standard case report form. Patient-reported outcome questionnaires (COPD-Q, COPD Assessment Test [CAT], modified Medical Research Council [mMRC] dyspnoea scale) were completed. Information on treatment exposure was also collected. If available, spirometry, chest computed tomography imaging, induced sputum, and lab test data were collected.

Outcomes

Co-primary outcomes of the study included mean rate of exacerbations, severe exacerbations requiring hospitalization or an emergency visit, severity of airflow limitation, COPD symptoms (assessed by CAT and mMRC), and COPD disease knowledge among patients (assessed by COPD-Q). The COPD-Q tool is a 13-point questionnaire that assesses patients' knowledge of COPD risk factors, clinical manifestations, medication, oxygen therapy, prevention, and prognosis [23–25]. It was specifically designed for individuals with low health literacy and fifth-grade reading level. Every correct answer was scored as 1 point and a higher score indicates a higher level of disease knowledge.

Secondary outcomes included disease severity (assessed by GOLD 2016 and 2017 combined assessment criteria [Groups A/B/C/D], as defined in the GOLD 2017 evidence-based strategy document [26]), treatment patterns (drug class, maintenance and exacerbation therapy), and medication adherence (actual drug taken days/follow-up days).

Statistical analysis

As this was an observational study, the data analysis was primarily descriptive. For continuous variables, mean, median, standard deviation (SD), and range were calculated. For categoric variables, frequency counts and percentages were provided. Descriptive statistics were used for the primary endpoints, and the annual exacerbation rate was estimated under the Poisson distribution assumption. Mean and standard error of the annual rates of exacerbation were calculated. A similar approach was used for the analyses of secondary outcomes. All statistical procedures were completed using Statistical Analysis System version 9.2 or later.

Results

Between 15 December 2017 and 6 August 2020, 5,097 patients were screened, of whom 5,013 were enrolled, and 4,978 included in the analysis (n = 2,597 from tertiary and n = 2,381 from secondary hospitals). Baseline patient demographics and clinical characteristics have been described previously [22]. Briefly, mean age was 66.2 years, and the majority of patients were male (79.5%). Patients were almost equally sampled from urban and rural areas (55.0% vs 45.0%) (Table 1). A large proportion of patients had smoking history: 2,556 (51.3%) former, 1,142 (22.9%) current, and 1,409 (28.3%) passive smokers. Approximately 20% of patients were exposed to dust, while 11.3% and 8.1% were exposed to biofuels and harmful gases, respectively. Concurrent respiratory diseases were reported in 25.9% of patients, with the most frequent being asthma (8.8%), respiratory infections (8.5%), and bronchiectasis (3.0%). The most common nonrespiratory comorbidities were hypertension (20.7%), coronary artery disease (6.3%), and diabetes mellitus (5.1%).

Table 1
Patient demographics and clinical characteristics at baseline

Characteristics	Patients with COPD at baseline (N = 4,978)
Male	3,959/4,978 (79.5)
Age (years), mean (SD)	66.2 (8.9)
BMI (kg/m^2), mean (SD)	22.97 (3.6)
Region of residence	
North	1,005/4,978 (20.2)
Northeast	623/4,978 (12.5)
East	1,248/4,978 (25.1)
South central	904/4,978 (18.2)
Southwest	596/4,978 (12.0)
Northwest	602/4,978 (12.1)
Residence area	
Urban	2,735/4,972 (55.0)
Rural	2,237/4,972 (45.0)
Smoking status	
Non-smoker	1,280/4,978 (25.7)
Current smoker	1,142/4,978 (22.9)
Former smoker	2,556/4,978 (51.3)
Passive smoker	1,409/4,975 (28.3)
Packs/year,* mean (SD)	42.1 (24.1)
Exposure to noxious particles or gases	
No exposure	3,397/4,978 (68.2)

BMI = body mass index; COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; SD = standard deviation.

Data are presented as n/N (%) unless stated otherwise. All percentages were calculated based on patients with available data. * Data were missing for 16 patients. † Reported respiratory disease history of patient's first-degree relatives. ‡ Requiring hospitalization or emergency room visit. § Diseases with a prevalence > 2%.

Characteristics	Patients with COPD at baseline (N = 4,978)
Dust	996/4,978 (20.0)
Harmful gas	404/4,978 (8.1)
Biofuels	564/4,978 (11.3)
Other noxious substances	73/4,978 (1.5)
A family history of respiratory disease[†]	**1,715/4,978 (34.5)**
History of ≥ 1 exacerbation in previous 12 months	**2,459/4,978 (49.4)**
Severe exacerbations[‡]	1,953/4,978 (39.2)
Concurrent respiratory diseases[§]	**1,287/4,978 (25.9)**
Asthma	437/4,978 (8.8)
Respiratory infection	422/4,978 (8.5)
Bronchiectasis	151/4,978 (3.0)
Non-respiratory comorbidities[§]	**1,981/4,978 (39.8)**
Hypertension	1,028/4,978 (20.7)
Coronary artery disease	313/4,978 (6.3)
Diabetes mellitus	247/4,978 (5.1)
Benign prostatic hyperplasia	168/4,978 (3.4)
Chronic gastritis	111/4,978 (2.2)
Severity of airflow limitation (GOLD stages)	
Stage I	458/4,518 (10.1)
Stage II	1,886/4,518 (41.7)
Stage III	1,558/4,518 (34.5)
Stage IV	616/4,518 (13.6)

BMI = body mass index; COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; SD = standard deviation.

Data are presented as n/N (%) unless stated otherwise. All percentages were calculated based on patients with available data. [*] Data were missing for 16 patients. [†] Reported respiratory disease history of patient's first-degree relatives. [‡] Requiring hospitalization or emergency room visit. [§] Diseases with a prevalence > 2%.

Characteristics	Patients with COPD at baseline (N = 4,978)
Combined assessment (GOLD 2017 groups)	
Group A	818/4,976 (16.4)
Group B	2,083/4,976 (41.9)
Group C	363/4,976 (7.3)
Group D	1,712/4,976 (34.4)
BMI = body mass index; COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; SD = standard deviation.	
Data are presented as n/N (%) unless stated otherwise. All percentages were calculated based on patients with available data. * Data were missing for 16 patients. † Reported respiratory disease history of patient's first-degree relatives. ‡ Requiring hospitalization or emergency room visit. § Diseases with a prevalence > 2%.	

At baseline, 458 (10.1%), 1,886 (41.7%), 1,558 (34.5%), and 616 (13.6%) patients were classified as having GOLD stage I, II, III, and IV, respectively. As per GOLD 2017 combined assessment criteria, Group B (n = 2,083 [41.9%]) constituted the largest group, followed by Group D (n = 1,712 [34.4%]). Severity distribution was influenced by hospital tier, with a lower proportion of patients in GOLD 2017 Group D and GOLD stages III–IV in tertiary than in secondary hospitals. Almost half of all patients experienced at least one exacerbation during the previous 12 months (n = 2,459 [49.4%]) (Table 1).

Acute exacerbations

Overall, the annual rate (per patient) of COPD exacerbations was 0.56 (95% confidence interval [CI]: 0.54–0.58). The annual rates of moderate (requiring systemic corticosteroids and/or antibiotics) and severe exacerbations were 0.17 (95% CI: 0.16–0.18) and 0.31 (95% CI: 0.29–0.33), respectively (Table 2 **and** Fig. 1).

Table 2
COPD exacerbations by baseline airway limitation severity and GOLD 2017 combined assessment at 1-year follow-up

	Total (N = 4,978)	Severity of airflow limitation (GOLD stages)			
		Stage I (N = 458)	Stage II (N = 1,886)	Stage III (N = 1,558)	Stage IV (N = 616)
Patients with ≥ 1 exacerbation	**1,535/4,978 (30.8)**	**94 (20.5)**	**514 (27.3)**	**524 (33.6)**	**279 (45.3)**
Moderate	505/4,978 (10.1)	35/94 (37.2)	212/514 (41.3)	166/524 (31.7)	76/279 (27.2)
Severe	960/4,978 (19.3)	45/94 (47.9)	282/514 (54.9)	350/524 (66.8)	210/279 (75.3)
Annual exacerbation rate (95% CI)	**0.56 (0.54–0.58)**	**0.33 (0.28–0.39)**	**0.47 (0.44–0.51)**	**0.64 (0.60–0.68)**	**0.90 (0.83–0.98)**
Moderate	0.17 (0.16–0.18)	0.12 (0.09–0.16)	0.18 (0.17–0.20)	0.18 (0.16–0.20)	0.25 (0.22–0.30)
Severe	0.31 (0.29–0.33)	0.15 (0.12–0.19)	0.22 (0.20–0.24)	0.38 (0.35–0.41)	0.58 (0.53–0.65)
		Combined assessment (GOLD 2017 groups)			
		Group A (N = 818)	**Group B (N = 2,083)**	**Group C (N = 363)**	**Group D (N = 1,712)**
Patients with ≥ 1 exacerbation		**137 (16.7)**	**484 (23.2)**	**119 (32.8)**	**794 (46.4)**
Moderate		63/137 (46.0)	179/484 (37.0)	45/119 (37.8)	218/794 (27.5)
Severe		49/137 (35.8)	267/484 (55.2)	74/119 (62.2)	569/794 (71.7)
Annual exacerbation rate (95% CI)		**0.26 (0.22–0.29)**	**0.36 (0.34–0.39)**	**0.62 (0.54–0.71)**	**0.93 (0.88–0.98)**
Moderate		0.12 (0.10–0.14)	0.13 (0.12–0.15)	0.24 (0.20–0.30)	0.24 (0.21–0.26)

CI = confidence interval; COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease.

Data are presented as n/N (%) unless stated otherwise. Rate and CI were estimated under the Poisson distribution assumption. Moderate = requiring systemic glucocorticosteroids, and/or antibiotics; Severe = hospitalization, emergency room visit or leading to death. All percentages were calculated based on patients with available data.

	Total (N = 4,978)	Severity of airflow limitation (GOLD stages)			
		Stage I (N = 458)	Stage II (N = 1,886)	Stage III (N = 1,558)	Stage IV (N = 616)
Severe		0.08 (0.06–0.10)	0.17 (0.15–0.18)	0.32 (0.27–0.38)	0.59 (0.55–0.63)

CI = confidence interval; COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease.

Data are presented as n/N (%) unless stated otherwise. Rate and CI were estimated under the Poisson distribution assumption. Moderate = requiring systemic glucocorticosteroids, and/or antibiotics; Severe = hospitalization, emergency room visit or leading to death. All percentages were calculated based on patients with available data.

The annual rates of exacerbation increased progressively for GOLD stages I–IV: 0.33 (95% CI: 0.28–0.39), 0.47 (95% CI: 0.44–0.51), 0.64 (95% CI: 0.60–0.68) and 0.90 (95% CI: 0.83–0.98), respectively. Similarly, in GOLD 2017 Groups A/B/C/D, annual exacerbation rates were 0.26 (95% CI: 0.22–0.29), 0.36 (95% CI: 0.34–0.39), 0.62 (95% CI: 0.54–0.71), and 0.93 (95% CI: 0.88–0.98), respectively (Table 2).

During the 12-month follow-up, 1535 (30.8%) patients experienced at least one exacerbation (moderate, n = 505 [10.1%]; severe, n = 960 [19.3%]). Among those, 47.9% (45/94), 54.9% (282/514), 66.8% (350/524), and 75.3% (210/279) of patients across GOLD stages I–IV, respectively, had a severe exacerbation. Similarly, the proportion of patients experiencing a severe exacerbation increased progressively across GOLD 2017 Groups A/B/C/D: 35.8% (49/137), 55.2% (267/484), 62.2% (74/119), and 71.7% (569/794), respectively (Table 2).

Change in forced expiratory volume in 1 second (FEV_1)

Mean (SD) change from baseline in FEV_1 was + 0.027 L (0.325). (Table 3). The mean (SD) change in FEV_1 across GOLD stages I–IV were: − 0.120 L (0.363), − 0.004 L (0.359), + 0.079 L (0.314), and + 0.141 L (0.249), respectively (**Table E1**).

Table 3
COPD disease characteristics at baseline and 1-year follow-up

Clinical characteristics	Patients with COPD (N = 4,978)	
	At baseline	At 1-year follow-up
COPD signs and symptoms	**4,975/4,978 (99.9)**	**4,198/4,978 (84.3)**
Dyspnoea	2,864/4,975 (57.6)	1,753/4,198 (41.8)
Wheezing	3,296/4,975 (66.3)	2,311/4,198 (55.1)
Chest tightness	3,324/4,975 (66.8)	2,024/4,198 (48.2)
Cough	4,037/4,975 (81.1)	2,809/4,198 (66.9)
Mucus purulence	4,011/4,975 (80.6)	2,761/4,198 (65.8)
CAT score	**4,976/4,978 (100)**	**4,184/4,978 (84.0)**
CAT total score, mean (SD)	14.6 (7.6)	10.6 (6.8)
Change from baseline, mean (SD)	–	−4.0 (7.2)
mMRC score	**4,976/4,978 (100)**	**4,178/4,879 (83.9)**
mMRC score, mean (SD)	1.4 (0.99)	1.1 (0.9)
Change from baseline, mean (SD)	–	−0.3 (1.0)
COPD-Q score	**4,973/4,978 (99.9)**	**4,142/4,978 (83.2)**
COPD-Q total score, mean (SD)	5.9 (2.0)	6.7 (2.4)
Change from baseline, mean (SD)	–	+ 0.7 (2.5)
Secondary hospitals	2,378/2,381 (99.9)	2,115/2,381 (88.8)
Secondary hospitals, mean (SD)	6.1 (1.9)	6.7 (2.6)
Change from baseline, mean (SD)	–	+ 0.6 (2.9)
Tertiary hospitals	2,595/2,597 (99.9)	2,027/2,597 (78.1)
Tertiary hospitals, mean (SD)	5.8 (2.1)	6.6 (2.1)
Change from baseline, mean (SD)	–	+ 0.8 (2.0)

CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; COPD-Q = COPD knowledge questionnaire; FEV_1 = forced expiratory volume in 1 second; mMRC = modified Medical Research Council; COPD-Q = COPD knowledge questionnaire; SD = standard deviation.

Data are presented as n/N (%) unless stated otherwise. All percentages were calculated based on patients with available data. * Change from baseline in FEV_1 was calculated based on patients with available FEV_1 measurements at baseline and 1-year follow-up.

Clinical characteristics	Patients with COPD (N = 4,978)	
	At baseline	At 1-year follow-up
FEV_1 [L]	**4,901/4,978 (98.5)**	**807/4,978 (16.2)**
FEV_1, mean (SD)	1.360 (0.586)	1.359 (0.600)
Change from baseline in FEV_1 [L]*	–	**792/4,978 (15.9)**
Change from baseline, mean (SD)	–	+ 0.027 (0.325)

CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; COPD-Q = COPD knowledge questionnaire; FEV_1 = forced expiratory volume in 1 second; mMRC = modified Medical Research Council; COPD-Q = COPD knowledge questionnaire; SD = standard deviation.

Data are presented as n/N (%) unless stated otherwise. All percentages were calculated based on patients with available data. * Change from baseline in FEV_1 was calculated based on patients with available FEV_1 measurements at baseline and 1-year follow-up.

COPD symptoms

The mean (SD) CAT score was 14.6 (7.6) at baseline, and 10.6 (6.8) at 1 year, with a mean (SD) change from baseline of − 4.0 (7.2). Mean (SD) mMRC score was 1.4 (0.99) and 1.1 (0.9) at baseline and 1 year, respectively, with a mean (SD) change from baseline of − 0.3 (1.0) (Table 3).

At 1 year, 41.8%, 48.2%, and 55.1% of patients had persistent dyspnoea, chest tightness and wheezing, respectively (Table 3). The proportion of patients with COPD symptoms progressively increased across GOLD stages I–IV (**Table E2**).

Treatment pattern and adherence

Inhaled corticosteroid (ICS) and long-acting β2-agonist (LABA) combinations (ICS/LABA, n = 848 [36.0%]), ICS/LABA plus long-acting muscarinic antagonist (LAMA; ICS/LABA + LAMA, n = 417 [17.7%]), and LAMA alone (n = 361 [15.3%]) were the most prescribed mono- or combination maintenance therapies (Table 4 **and** Fig. 2). The prescription rates of ICS-containing therapies (ICS/LABA or ICS/LABA + LAMA) differed between GOLD stages I–IV; ICS/LABA therapy was prescribed more frequently in patients with mild disease (stages I–IV: 46.3%, 36.3%, 32.9%, 30.5%, respectively), while ICS/LABA + LAMA therapy was prescribed more frequently in patients with severe disease (11.0%, 13.3%, 20.7%, 27.2%, respectively). However, the prescription of ICS/LABA and ICS/LABA + LAMA were consistent across GOLD 2017 Groups A–D (ICS/LABA: 35.4%, 35.3%, 38.6%, 36.4%, respectively; ICS/LABA + LAMA: 18.0%, 16.8%, 14.3%, 19.0%, respectively) (Table 4 **and Table E3**).

Table 4
Distribution of prescribed COPD maintenance therapies by baseline airway limitation severity at 1-year follow-up

	Severity of Airflow Limitation (GOLD stages)				Total (N = 4,978)
	Stage I (N = 458)	Stage II (N = 1,886)	Stage III (N = 1,558)	Stage IV (N = 616)	
Mono or combination therapy*	n = 164	n = 827	n = 781	n = 367	n = 2,358
ICS	0	2 (0.2)	1 (0.1)	2 (0.5)	5 (0.2)
ICS/LABA	76 (46.3)	300 (36.3)	257 (32.9)	112 (30.5)	848 (36.0)
ICS/LABA + SABA	3 (1.8)	7 (0.8)	10 (1.3)	3 (0.8)	25 (1.1)
ICS/LABA + methylxanthines	5 (3.0)	26 (3.1)	23 (2.9)	10 (2.7)	65 (2.8)
ICS/LABA + TCM	3 (1.8)	7 (0.8)	3 (0.4)	2 (0.5)	16 (0.7)
ICS/LABA + LAMA	18 (11.0)	110 (13.3)	162 (20.7)	100 (27.2)	417 (17.7)
ICS/LABA + LAMA + SABA	0	5 (0.6)	5 (0.6)	5 (1.4)	18 (0.8)
ICS/LABA + LAMA + methylxanthines	1 (0.6)	8 (1.0)	18 (2.3)	7 (1.9)	35 (1.5)
ICS/LABA + LAMA + TCM	1 (0.6)	8 (1.0)	10 (1.3)	6 (1.6)	27 (1.1)
LAMA	28 (17.1)	166 (20.1)	109 (14.0)	25 (6.8)	361 (15.3)
LAMA + SABA	0	0	3 (0.4)	2 (0.5)	5 (0.2)
LAMA + methylxanthines	1 (0.6)	12 (1.5)	11 (1.4)	6 (1.6)	31 (1.3)
LAMA + TCM	2 (1.2)	19 (2.3)	5 (0.6)	2 (0.5)	31 (1.3)
LAMA + LABA	2 (1.2)	10 (1.2)	9 (1.2)	6 (1.6)	27 (1.1)
LAMA + LABA + SABA	0	1 (0.1)	0	0	1 (0.0)
LAMA + LABA + methylxanthines	0	1 (0.1)	0	0	1 (0.0)

COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroid; LABA = long-acting β2-agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting β2-agonist; SAMA = short-acting muscarinic antagonist; TCM = traditional Chinese medicine.

Data are presented as n (%) unless stated otherwise. * Medications classified by drug class. † This class denotes prescriptions without ICS, LABA, ICS/LABA, or LAMA.

	Severity of Airflow Limitation (GOLD stages)				Total
	Stage I (N = 458)	Stage II (N = 1,886)	Stage III (N = 1,558)	Stage IV (N = 616)	(N = 4,978)
LAMA + LABA + TCM	0	8 (1.0)	5 (0.6)	4 (1.1)	17 (0.7)
LABA	1 (0.6)	10 (1.2)	6 (0.8)	4 (1.1)	21 (0.9)
SABA	3 (1.8)	13 (1.6)	17 (2.2)	10 (2.7)	49 (2.1)
SAMA	0	2 (0.2)	1 (0.1)	0	3 (0.1)
SABA/SAMA	0	0	1 (0.1)	2 (0.5)	3 (0.1)
Methylxanthines	4 (2.4)	12 (1.5)	14 (1.8)	6 (1.6)	41 (1.7)
Methylxanthines + SABA	0	2 (0.2)	5 (0.6)	1 (0.3)	13 (0.6)
Methylxanthines + TCM	0	9 (1.1)	9 (1.2)	3 (0.8)	27 (1.1)
TCM	2 (1.2)	17 (2.1)	19 (2.4)	9 (2.5)	53 (2.2)
None of the medications described above	9 (5.5)	23 (2.8)	14 (1.8)	7 (1.9)	58 (2.5)
Medications used in any form*	n = 164	n = 827	n = 781	n = 367	n = 2,358
ICS	2 (1.2)	5 (0.6)	6 (0.8)	4 (1.1)	19 (0.8)
ICS/LABA	112 (68.3)	501 (60.6)	520 (66.6)	259 (70.6)	1534 (65.1)
LABA	4 (2.4)	52 (6.3)	50 (6.4)	25 (6.8)	133 (5.6)
LAMA	54 (32.9)	365 (44.1)	354 (45.3)	174 (47.4)	1019 (43.2)
SABA	8 (4.9)	40 (4.8)	61 (7.8)	37 (10.1)	169 (7.2)
SAMA	1 (0.6)	9 (1.1)	12 (1.5)	8 (2.2)	32 (1.4)
SABA/SAMA	0	3 (0.4)	3 (0.4)	5 (1.4)	11 (0.5)

COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroid; LABA = long-acting β2-agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting β2-agonist; SAMA = short-acting muscarinic antagonist; TCM = traditional Chinese medicine.

Data are presented as n (%) unless stated otherwise. * Medications classified by drug class. † This class denotes prescriptions without ICS, LABA, ICS/LABA, or LAMA.

	Severity of Airflow Limitation (GOLD stages)				Total
	Stage I (N = 458)	Stage II (N = 1,886)	Stage III (N = 1,558)	Stage IV (N = 616)	(N = 4,978)
Methylxanthines	14 (8.5)	94 (11.4)	116 (14.9)	56 (15.3)	303 (12.8)
Mucolytics	22 (13.4)	155 (18.7)	142 (18.2)	67 (18.3)	403 (17.1)
TCM	10 (6.1)	89 (10.8)	79 (10.1)	34 (9.3)	234 (9.9)
Others	25 (15.2)	156 (18.9)	174 (22.3)	86 (23.4)	456 (19.3)
Neither ICS nor long-acting bronchodilator†	18 (11.0)	84 (10.2)	91 (11.7)	43 (11.7)	273 (11.6)

COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroid; LABA = long-acting β2-agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting β2-agonist; SAMA = short-acting muscarinic antagonist; TCM = traditional Chinese medicine.

Data are presented as n (%) unless stated otherwise. * Medications classified by drug class. † This class denotes prescriptions without ICS, LABA, ICS/LABA, or LAMA.

Despite having more symptoms and/or being at increased risk of exacerbations, 111 (12.1%) patients in GOLD 2017 Group B, 19 (10.1%) in Group C, and 123 (13.1%) in Group D were not prescribed ICS or long-acting bronchodilators (**Table E3**). In addition, the prescription rates for ICS-containing therapy among patients experiencing exacerbations did not differ during the 1-year follow-up (Table 5). Among patients in GOLD Groups C and D who experienced at least one exacerbation during the 1-year follow-up, 53.8% (64/119) and 63.6% (505/794), respectively, were prescribed ICS-containing therapy. This included 18 (15.1%) and 182 (22.9%) patients, respectively, receiving triple therapy (ICS/LABA + LAMA).

Table 5
ICS prescriptions in patients with COPD exacerbations by baseline GOLD 2017 combined assessment at 1-year follow-up

	Combined assessment (GOLD 2017 groups)				
	Group A (N = 818)	Group B (N = 2,083)	Group C (N = 363)	Group D (N = 1,712)	Total (N = 4,978)
Patients with ≥ 1 exacerbation in the 12 months before baseline	100 (12.2)	283 (13.6)	363 (100)	1,712 (100)	2,459 (49.4)
ICS or ICS/LABA prescribed at baseline	61 (61.0)	158 (55.8)	221 (60.9)	1,080 (63.1)	1,521 (61.9)
ICS/LABA + LAMA prescribed at baseline	26 (26.0)	62 (21.9)	69 (19.0)	385 (22.5)	543 (22.1)
Patients with ≥ 1 exacerbation during the 1-year study follow-up (from baseline to study end)	137 (16.7)	484 (23.2)	119 (32.8)	794 (46.4)	1,535 (30.8)
ICS or ICS/LABA prescribed during 1-year study follow-up	85 (62.0)	299 (61.8)	64 (53.8)	505 (63.6)	954 (62.1)
ICS/LABA + LAMA prescribed during 1-year study follow-up	34 (24.8)	118 (24.4)	18 (15.1)	182 (22.9)	353 (23.0)

COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroid; LABA = long-acting β2-agonist; LAMA = long-acting muscarinic antagonist.

Data are presented as n (%) unless stated otherwise. All percentages were calculated based on patients with available data.

Mean (SD) adherence (actual drug taken days/follow-up days) for long-acting inhalers was 59.0% (34.3). COPD medication adherence was similar across GOLD stages and GOLD 2017 groups (**Table E4**). Mean COPD medication adherence ranged from 53.5–64.7% for GOLD stages I–IV, and from 57.7–60.7% for GOLD 2017 Groups A–D.

Patient COPD knowledge

Overall mean COPD-Q scores were 5.9 at baseline, and 6.7 at 1-year follow-up. The latter ranged from 5.2 to 7.4 across geographical regions and did not differ between tertiary and secondary hospitals, indicating patients' poor understanding of COPD. Overall, the mean (SD) change from baseline in COPD-Q score at 1-year follow-up was + 0.7 (2.5), and the corresponding change for tertiary and secondary hospitals was + 0.8 (2.0) and + 0.6 (2.9), respectively (Table 3).

Discussion

REAL is the first nationwide study designed to collect prospective longitudinal data on the management and clinical outcomes of Chinese outpatients with COPD managed at secondary and tertiary hospitals. Overall, findings from the study revealed a high burden of severe exacerbations, airflow limitation, and symptoms in this population. This high disease burden may be explained by the lack of adherence to guideline-recommended treatment among healthcare providers, as well as poor medication adherence and disease awareness among patients, highlighting the need for more effective management.

Our study enrolled a nationally representative population of adults aged ≥ 40 years with COPD. The majority of patients in our study were male, which is consistent with previous studies. Nationwide cross-sectional studies in China have demonstrated a higher prevalence of COPD among males [21, 27], while the prevalence is more similar between the sexes in Europe and the US [28]. These data further demonstrate that the population in the REAL study is nationally representative. Compared with previous studies [16, 29], our study also comprised a larger patient population and included patients from a broader range of geographic regions.

Most COPD outpatients had moderate-to-very-severe airflow limitation, with GOLD stages II–IV accounting for 90% of the study population. More than one-third of patients were classified as GOLD Group D, with persistent symptoms and a high risk of exacerbations. This could be explained by the enrolment of patients from secondary and tertiary hospitals, where patients with mild disease are not routinely managed. This could also be due to patients at early stages of the disease with mild symptoms not seeking medical attention for COPD symptoms or not being diagnosed by physicians [30].

One of the key goals of the study was to collect data on the annual exacerbation rate. Overall, about 30% of patients experienced at least one exacerbation during the 1-year follow-up, which was lower than that reported in the year prior to study enrolment (49.4%). The annual exacerbation rates in our study are lower than those reported previously (37–71%) [31–33], which may be explained by underreporting of exacerbations, particularly those of moderate severity. Previous studies have shown that a large number (50–68%) of COPD exacerbations are not reported and are, therefore, left untreated, which increases the risk of disease progression [19, 20]. In our study, a high proportion of patients experienced severe exacerbations regardless of COPD severity. Our findings highlight the need to optimize the management of patients with COPD, and indicate there may be a need to increase understanding of risk factors for exacerbation to facilitate earlier detection and reduce treatment delays. This in turn may prevent exacerbations from becoming severe. The ECLIPSE study has shown that patients with severe COPD have a history of frequent exacerbations, and that past exacerbation may predict the occurrence of future exacerbations [34]. To facilitate increased knowledge of exacerbations among physicians, further analysis of risk factors for COPD exacerbation in the REAL study is underway and will subsequently published.

Underreporting of COPD exacerbations may have been more marked during the COVID-19 pandemic, which led to fewer hospital visits. Conversely, COVID-19 control measures, such as use of masks and implementation of lockdowns, may have had a positive effect on COPD outcomes due to reduced upper

respiratory tract infections. Accordingly, a national level analysis from the UK showed a 48% reduction in emergency admissions for COPD exacerbations during the UK-wide COVID-19 lockdown [35]. Moreover, reporting of moderate exacerbations in this study could have been influenced by variations in the standard indications for COPD hospitalisation across China, with less strict administration and control.

A large proportion of patients had persistent COPD symptoms, including dyspnoea, wheezing, chest tightness, and cough, throughout the study follow-up. Presence of shortness of breath, wheezing, or chest tightness may indicate disease progression, as these symptoms were more common in severe/very severe cases than in mild/moderate cases. Understanding the symptoms associated with COPD may help improve physician's disease awareness and facilitate early intervention before substantial disease progression. Symptoms including dyspnoea, wheezing, and chronic cough were previously shown to be associated with exacerbation occurrence in the ECLIPSE study [34]. Further analysis of symptoms associated with exacerbation severity in the REAL study will subsequently published.

The substantial burden of severe exacerbations, airflow limitation, and persistent symptoms in this study suggest suboptimal management of COPD in China. Accordingly, we found substantial discrepancies between the real-world treatment patterns and the treatment guidelines for clinical practice [15], supporting previous findings [16, 29] but providing evidence that these discrepancies are likely nationwide. The most prescribed maintenance therapies in the REAL study were ICS/LABA, ICS/LABA + LAMA, and LAMA; however, their prescription rates varied (range: 15.3–36.0%). In addition, 11.6% of patients were not prescribed ICS or long-acting bronchodilators, the mainstay long-term inhaled medications for symptom alleviation and exacerbation risk reduction. Compared with baseline, there was an improvement in the prescription rate of ICS/LABA at 1 year (26.4% vs 36.0%); however, prescription rates of ICS/LABA + LAMA (17.5% vs 17.7%) and LAMA (15.1% vs 15.3%) were comparable between baseline and follow-up, respectively [36]. Notably, prescription rates for ICS-containing therapies were similar across GOLD groups, indicating that they were not prescribed based on exacerbations risk. Conversely, prescription rates for ICS-containing therapies differed based on airflow limitation (ICS/LABA therapy prescribed more frequently in patients with mild disease and ICS/LABA + LAMA in patients with stage III or IV disease). These data may explain the improved FEV_1 in patients with GOLD stages III and IV disease but not those with GOLD stages I and II disease. These findings suggest that the main goal of COPD maintenance therapy in China is to relieve symptoms, and that attention to history of acute exacerbation is lacking. Indeed, COPD maintenance therapy is mostly prescribed based on pulmonary function rather than exacerbation risk in China, given that exacerbation risk evaluation is more complex [14]. These data, however, highlight the need for physicians to prescribe treatment based on exacerbation risk to prevent disease progression and improve patient outcomes.

Our findings reinforce those in previous studies and further emphasize the need for COPD management and treatment standardization nationwide in accordance with existing guidelines. In addition, our findings support the importance of increasing physicians' disease and symptom awareness to enable early intervention and improve treatment based on exacerbation risk. Among patients, treatment adherence is key, and this has been shown to be influenced by patients' understanding of their disease [37]. We and

others have demonstrated that patients with COPD are poorly informed about their disease and its treatment [14]. It is thus critical to also put in place strategies to improve patients' awareness and knowledge of COPD. To fully address the challenges of COPD management in China, substantial attention should be on improving both physicians' and patients' disease knowledge.

The study results should be viewed in the context of the following limitations. Firstly, patients with early-stage COPD and those with mild symptoms were underrepresented as the study only included patients who were diagnosed with COPD and visited the outpatient respiratory department of secondary and tertiary hospitals. This suggests that the symptoms, exacerbation rates, and treatment patterns reported in this study did not reflect that of patients with mild COPD. It is important for these patients to be characterised to help improve early detection and intervention of the disease. Secondly, the COVID-19 pandemic may have discouraged patients with COPD from visiting the hospitals, which may have resulted in underreporting of outcomes. Thirdly, the fixed-dose combinations of LABA/LAMA dual therapy and ICS/LABA/LAMA triple therapy were not available in China during the study period. In addition, the implementation of the national hierarchical medical system allowed some patients to obtain their prescription medications from a community hospital, and the prescription rates in the community hospitals were not captured in the reporting of treatment patterns in this study. These factors may impact the extent to which our findings represent current treatment patterns among COPD patients in China. Nonetheless, our findings reinforce the discrepancies identified in previous studies between real-world clinical practice and current treatment guidelines, and further demonstrate that standardisation efforts should be rolled out nationwide. Finally, data were confined to examinations and tests performed in routine clinical practice; thus, not all assessment data were available.

Conclusions

In conclusion, findings from this large real-world study revealed that most Chinese outpatients with COPD have moderate-to-very-severe airflow limitation, with a high burden of acute exacerbations and symptoms. Overall, we reinforce the findings of previous studies but reveal that substantial inconsistencies between clinical practice and international COPD guidelines are present across China. This is coupled with poor disease knowledge, suboptimal medication adherence, and low uptake of regular examinations among patients. Evidence-based prescription of ICS-containing treatment in patients at high risk of exacerbation, as well as treatment adherence, need to be improved. There is an urgent need for standardization of outpatient management of COPD in China and improvement of both physicians' and patients' disease knowledge. Based on the study findings, any approach in addressing the challenges of COPD management in China should be nationwide.

Abbreviations

BMI: Body mass index; CI: Confidence interval; CAT: Chronic obstructive pulmonary disease assessment test; COPD: Chronic obstructive pulmonary disease; COPD-Q: Chronic obstructive pulmonary disease questionnaire; COVID-19: Coronavirus disease 2019; FEV_1: Forced expiratory volume in 1 second; GOLD:

Global Initiative for Chronic Obstructive Lung Disease; GPP3: Good Publication Practice; ICS: Inhaled corticosteroid; LABA: Long-acting β2-agonist; LAMA: Long-acting muscarinic antagonist; mMRC: Modified Medical Research Council; SABA: Short-acting β2-agonist; SD: Standard deviation; TCM: Traditional Chinese medicine

Declarations

Ethics approval and consent to participate

The study was designed and conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practices, Good Pharmacoepidemiology Practices, and in line with the regulations and guidelines governing medical practice and ethics in China. The study was approved in writing by the Institutional Review Board or Independent Ethics Committee. All patients in this study provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

TY, BCai, BCao, JK, FW, YC, WJ, and CW declare that they have no competing interests. YF is an employee of AstraZeneca China.

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Authors' contributions

All authors had access to all relevant data. All authors contributed to the study conceptualization and design, data collection, and analysis and interpretation, as well as manuscript draft, review, and approval.

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Figures

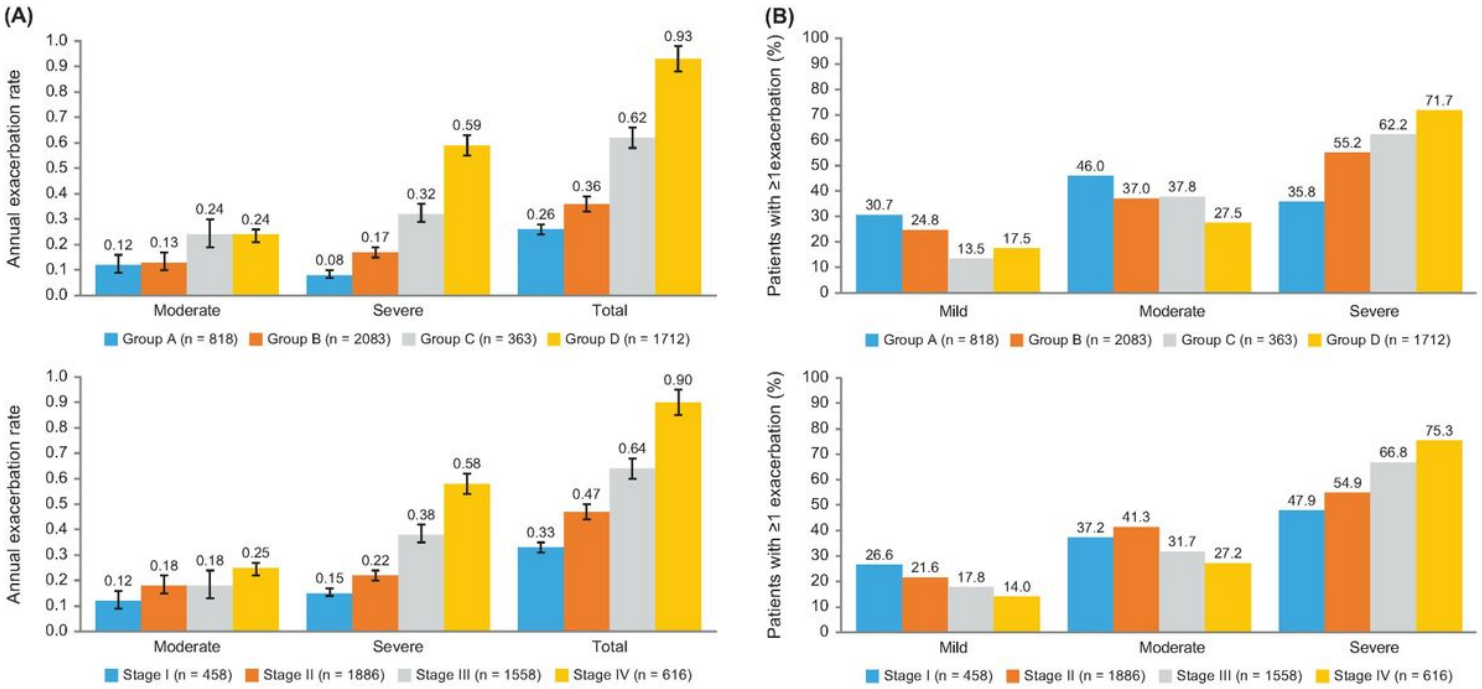

Figure 1

Acute exacerbations during 1-year follow-up.

(A) Annual exacerbation rate by airway limitation severity (GOLD stages) and combined assessment (GOLD 2017 groups). (B) Proportion of patients experiencing at least one COPD exacerbations during 1-year follow-up by airway limitation severity (GOLD stages) and combined assessment (GOLD 2017 groups). Rates and confidence intervals are estimated under the Poisson distribution assumption. Mild = requiring an increase in rescue medication ≥3 puffs/day for at least 2 consecutive days; Moderate = requiring systemic glucocorticosteroids, and/or antibiotics; Severe = hospitalization, emergency room visit, or leading to death.

COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease.

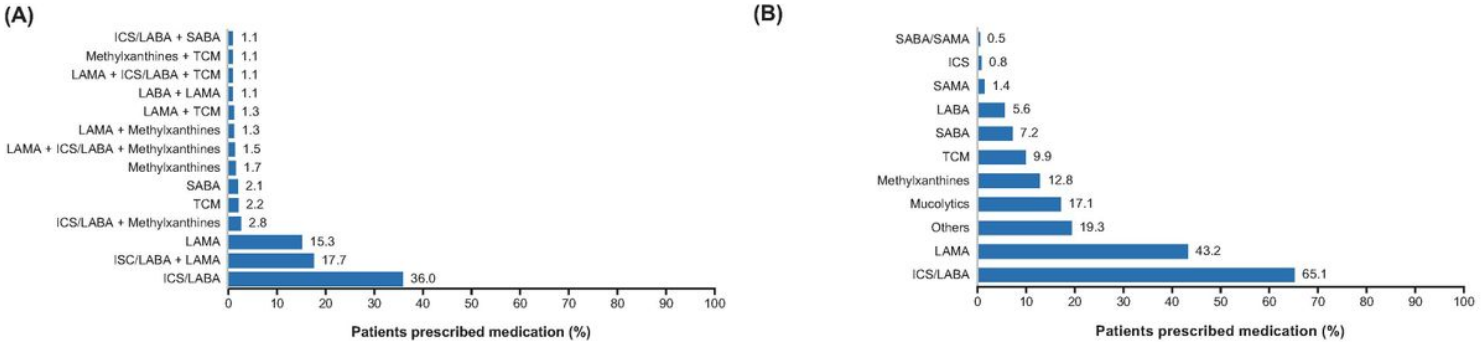

Figure 2

Distribution of maintenance medications for COPD at 1-year follow-up.

(A) Distribution of prescribed mono- and combination maintenance therapies for COPD. Mono- or combination therapies with bronchodilators and/or ICS (prescribed for ³1% of patients) are shown, with no prohibition of use with mucolytics and other classes of medication. (B) Distribution of medications prescribed in any form for COPD. Percentages of patients prescribed each class of medication are indicated.

COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; LABA = long-acting β2-agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting β2-agonist; SAMA = short-acting muscarinic antagonist; TCM = traditional Chinese medicine.

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