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ORIGINAL RESEARCH

The Characteristics of Airflow Limitation and Future Exacerbations in Different GOLD Groups of COPD Patients

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Background: The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 separated pulmonary function from combined assessment. We aimed to analyze the characteristics of airflow limitation and future exacerbations in different GOLD groups of chronic obstructive pulmonary disease (COPD) patients.

Methods: For this prospective observational study, stable COPD outpatients were enrolled and divided into Groups A, B, C and D based on GOLD 2017, and followed-up for 18 months. Data on demographics, pulmonary function, COPD assessment test (CAT), Clinical COPD Questionnaire (CCQ), modified Medical Research Council (mMRC), exacerbations, mortality and treatments were collected. A post-bronchodilator ratio of forced expiratory volume in one second to forced vital capacity <0.70 confirms the presence of airflow limitation.

Results: A total of 993 subjects were classified into Groups A (n = 170, 17.1%), B (n = 360, 36.3%), C (n = 122, 12.3%), and D (n = 341, 34.3%). There were significant differences in mMRC, CAT, CCQ, exacerbations and hospitalizations rates among the different groups ($P < 0.001$). Groups B and D had more severe airflow limitation than Groups A and C ($P < 0.05$). In the same groups with different severity of airflow limitation, the differences were mainly observed in body mass index, CAT, CCQ and treatment with long-acting muscarinic antagonist (LAMA) and LAMA + long-acting β2-agonist + inhaled corticosteroid ($P < 0.05$). After 18 months of follow-up, the exacerbations and hospitalizations rates were significantly different among different groups ($P < 0.05$). However, in the same groups with different airflow limitation severity, the mortality rates and number of exacerbations, hospitalizations and frequent exacerbators showed no differences.

Conclusion: In the GOLD groups, different severity of airflow limitation had no impact on future exacerbations and mortality rate. It implies that pulmonary function is not a good indicator for predicting exacerbation.

Keywords: chronic obstructive pulmonary disease, Global Initiative for Chronic Obstructive Lung Disease, pulmonary function, exacerbation

Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease, characterized by respiratory symptoms and persistent airflow limitation.[1,2] It is the most serious chronic respiratory disease, and has become the fifth highest contributing disease to the global economic burden, as well as the third leading cause of mortality in the world.[3]

The goal of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) program is to produce recommendations for the management of COPD based on the

best scientific information available. The first edition of GOLD was released in 2001 and has been revised annually.[4] Until 2011, GOLD evaluated COPD patients based on symptoms, severity of airflow limitation, exacerbation risk. According to combined COPD assessment, patients were divided into Groups A, B, C and D.[5] However, compared with pulmonary function classification, the combined COPD assessment cannot better predict mortality and other important clinical outcomes.[6–8] Therefore, the GOLD 2017 revised the assessment tool and separated pulmonary function. ABCD groups were only determined based on COPD assessment test (CAT) or modified Medical Research Council (mMRC), and exacerbation history.[9]

The pulmonary function test is the most important measurement of airflow limitation. A post-bronchodilator ratio of forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) <0.70 can be interpreted as airflow limitation. FEV1 is an important pulmonary function parameter, which underlies most of the clinical trial evidence about treatment efficacy in COPD is based on.[10,11] Pulmonary function results remain vital for the diagnosis and treatment of COPD. However, whether pulmonary function can be used as a good indicator to predict exacerbation is unclear.

Kim et al[12] found that there was no difference in the rate of decline in pulmonary function among different groups categorized by GOLD 2014 assessment tools. However, the characteristics of pulmonary function in different groups according to GOLD 2017 are unclear. In the present study, the aim was to analyze the characteristics of airflow limitation and future exacerbations in different GOLD groups of COPD patients.

Patients and Methods

Study Design and Subjects

This was a multicenter, prospective observational study, based on data collected as part of the Chronic Pulmonary Diseases Database setup by the Second Xiangya Hospital of Central South University (Hunan, China) (Registration number: ChiCTR-POC-17010431). Patients were enrolled from October 2017 to February 2019. All patients were followed-up for 18 months. According to criteria of GOLD 2017, COPD was confirmed when an FEV1/FVC ratio <0.70 was obtained, following the inhalation of 400 μg of salbutamol aerosol. Exclusion criteria were patients with other chronic respiratory diseases, such as bronchiectasis, asthma, lung cancer or pneumonia.

This study was approved by the local Ethics Committee of the Second Xiangya Hospital of Central South University and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent in this study.

Data Collection

The collected data included age, sex, schooling level, body mass index (BMI), smoking history, biofuel and occupational exposure history, CAT, mMRC, Clinical COPD Questionnaire (CCQ), pulmonary function data, exacerbations, hospitalizations and treatments. After 18 months of follow-up, data on exacerbations, hospitalizations and mortality were collected. As for smoking history, we defined "Never-smoker" as smoking exposure less than 10 pack-years, "Ex-smoker" as not less than 10 pack-years but smoking cessation more than 6 months.[13]

Definition of Exacerbation

In this study, an exacerbation was defined as an acute worsening of respiratory symptoms that resulted in the need for additional therapy (including antibiotics, oral corticosteroids or require hospitalization).[14] Frequent exacerbators were patients who suffered at least two exacerbations or one hospitalization during follow-up.

Definition of Biofuel and Occupational Exposure

Biofuel exposure was defined as using biomass fuels (wood, grass, charcoal, or crop residues) for cooking or heating for at least 2 hours per day for at least 1 year. Occupational exposure was defined as exposure to dust, gases, chemical substances, paints, or metals at work for at least 8 hours per day for at least 1 year.[15]

Classification of Combined COPD Assessment

According to GOLD 2017 guidelines, patients were assigned to four categories. Briefly, Group A, 0 to 1 exacerbation per year, no hospitalization, CAT score < 10 or mMRC score of 0 to 1; Group B, 0 to 1 exacerbation per year, no hospitalization, CAT score ≥ 10 or mMRC score ≥ 2; Group C, exacerbations ≥ 2 or hospitalization ≥ 1 per year, CAT score < 10 or mMRC score of 0 to 1; Group D, exacerbations ≥ 2 or hospitalization ≥ 1 per year, CAT score ≥ 10 or mMRC

score ≥ 2.[16] Then, each group was divided into two subgroups including GOLD I–II and III–IV.

Classification in Severity of Airflow Limitation

Severity of airflow limitation was based on the post-bronchodilator FEV1% predicted (FEV1%) as follows: GOLD I, FEV1% ≥ 80; GOLD II, FEV1% 50–79; GOLD III, FEV1% 30–49; GOLD IV, FEV1% < 30 according to GOLD 2017 guidelines.[16]

Pulmonary Function Data

The pulmonary function test was measured by a spirometer (MasterScreen-Body/Diff, CareFusion, Germany). According to the American Thoracic Society guidelines, the following parameters were included after a bronchodilator test: FEV1%, FVC%, FEV1/FVC, maximal expiratory flow (MEF)25%, MEF75%, peak expiratory flow (PEF)% and bronchodilator test (positive or negative). The bronchodilator test was performed 20 minutes after inhaling 400 μg of salbutamol aerosol and by a professional technician.

Statistical Analysis

Statistical analyses were performed using SPSS 26 (IBM Corporation, Armonk, NY, USA). The data was expressed as the mean ± standard deviation, or as the median and interquartile range. The Pearson's chi-squared test was used to analyze categorical variables. Comparisons of continuous variables were performed using independent-samples *t*-test or one-way analysis. The least significant difference *t*-test was used for pair-wise comparisons. The non-parametric test was used for non-normal distribution or uneven variance. A value of $P < 0.05$ was considered statistically significant.

Results

Baseline Demographic and Clinical Characteristics (N = 993)

A total of 993 patients were analyzed (Figure 1). According to GOLD 2017, 17.1, 36.3, 12.3 and 34.3% of patients were allocated to Groups A, B, C and D, respectively. The data on demographic and clinical characteristics are shown in Table 1. The mean age of the enrolled patients from Groups A to D were significantly different ($P < 0.001$). There were more current-smokers in Groups A and C ($P < 0.05$). There were higher CAT and CCQ scores in Groups B and D ($P < 0.05$). The proportion of long-acting muscarinic antagonist (LAMA) was higher in Groups A and C, while LAMA + long-acting β2-agonist (LABA) + inhaled corticosteroid (ICS) was higher in Groups B and D ($P < 0.05$). There were higher exacerbations and hospitalizations rates in Groups C and D ($P < 0.05$). The proportions of patients in Groups A, B, C and D that suffered an exacerbation once per year were 13.5, 13.1, 50.8 and 26.7%, respectively. The proportion of patients who were never hospitalized in Groups A, B, C and D were 100, 100, 28.7 and 31.4%, respectively.

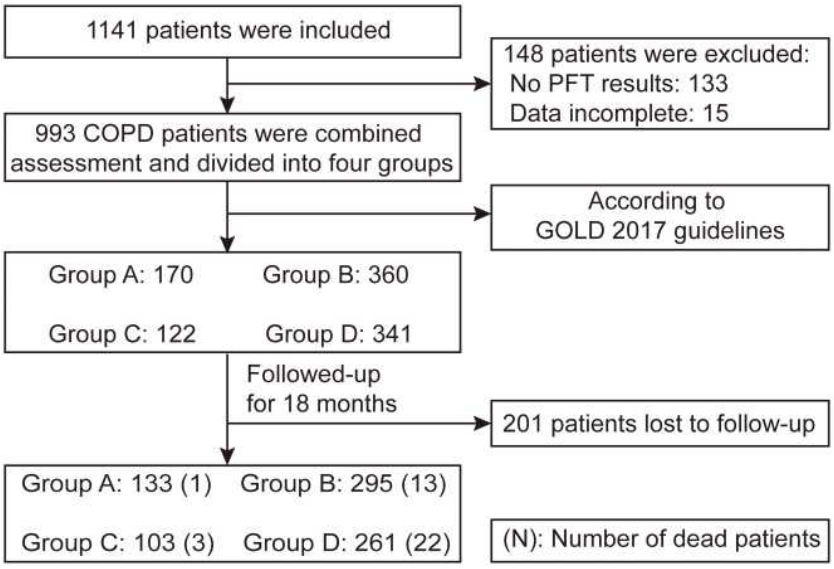

Figure 1 Flow chart of study inclusion. Groups A to D were categories according to GOLD 2017 guidelines.
Abbreviations: COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; PFT, pulmonary function test.

Table 1 The Distribution of Baseline Demographic and Clinical Characteristics in Different Groups (N = 993)

Variables	Group A (n = 170)	Group B (n = 360)	Group C (n = 122)	Group D (n = 341)	P value
Age (years)	61.5 ± 7.9 * &	65.1 ± 8.1 ¶	63.0 ± 9.1 ♠	66.8 ± 8.0 ▲	<0.001
Female, n (%)	21 (12.4)	40 (11.1)	9 (7.4)	42 (12.3)	0.488
Schooling level, n (%)					
Primary school	59 (34.7) * # &	148 (41.1)	56 (45.9) ♠	160 (46.9) ▲	0.050
Junior high school	57 (33.5)	132 (36.7)	48 (39.3)	120 (35.2)	0.751
High school	36 (21.2) * # &	63 (17.5) ¶	11 (9.0) ♠	47 (13.8) ▲	0.021
University	18 (10.6) * # &	17 (4.7) ¶	7 (5.8) ♠	14 (4.1)	0.019
BMI (kg/m^2)	23.1 ± 3.6	22.7 ± 3.9	22.6 ± 3.4	22.2 ± 3.7	0.071
Smoking history, n (%)					
Never-smoker	30 (17.6)	65 (18.0)	19 (15.6)	69 (20.2)	0.681
Ex-smoker	43 (25.3)	119 (33.1)	36 (29.5)	126 (37.0)	0.054
Current-smoker	97 (57.1) * &	176 (48.9) ¶	67 (54.9) ♠	146 (42.8) ▲	0.010
Smoke (pack/year) (Median, IQR)	30 (30)	32 (30)	36.5 (31.25)	30 (30)	0.357
Biofuel exposure, n (%)					<0.001
No	127 (74.7) * # &	213 (59.2)	73 (59.8)	180 (52.8)	
Occupational exposure, n (%)					0.471
No	111 (65.3)	229 (63.6)	70 (57.4)	207 (60.7)	
CAT (Mean ± SD)	10.3 ± 4.8 * # &	16.6 ± 5.1 ¶	13.6 ± 5.0 ♠	19.2 ± 5.8 ▲	<0.001
mMRC (Median, IQR)	1 (0) * &	2 (1) ¶	1 (0) ♠	3 (1) ▲	<0.001
CCQ (Mean ± SD)	15.9 ± 5.9 * # &	22.8 ± 5.7 ¶	19.2 ± 5.7 ♠	25.5 ± 5.8 ▲	<0.001
Treatments, n (%)					
Any COPD medication	157 (92.4) * # &	351 (97.5) ¶	115 (94.3)	328 (96.2) ▲	0.039
LAMA	87 (51.2) * &	123 (34.2) ¶	60 (49.2) ♠	111 (32.6)	<0.001
LABA+ICS	12 (7.1)	33 (9.2)	10 (8.2)	18 (5.3)	
LAMA+LABA	1 (0.6)	2 (0.6)	0 (0)	4 (1.2)	0.716
LAMA+LABA+ICS	55 (32.6) * &	190 (52.8) ¶	43 (35.3) ♠	195 (57.2)	<0.001
Exacerbations in the past year (Mean ± SD)	0.1 ± 0.3 # &	0.1 ± 0.3 ¶	2.5 ± 2.6 ♠	3.5 ± 4.1 ▲	<0.001
Exacerbations in the past year, n (%)					<0.001

(*Continued*)

Table 1 (Continued).

Variables	Group A (n = 170)	Group B (n = 360)	Group C (n = 122)	Group D (n = 341)	P value
0	147 (86.5) # &	313 (86.9) ¶	0 (0)	0 (0) ▲	
1	23 (13.5) # &	47 (13.1) ¶	62 (50.8) ♠	91 (26.7) ▲	
≥ 2	0 (0) # &	0 (0) ¶	60 (49.2) ♠	250 (73.3) ▲	
Hospitalizations in the past year (Mean ± SD)	0 # &	0 ¶	0.9 ± 1.0	1.4 ± 1.5 ▲	<0.001
Hospitalizations in the past year, n (%)					<0.001
0	170 (100) # &	360 (100) ¶	35 (28.7)	107 (31.4) ▲	
≥ 1	0 (0) # &	0 (0) ¶	87 (71.3)	234 (68.6) ▲	

Notes: *Compared with the Group B, P < 0.05; #Compared with the Group C, P < 0.05; &Compared with the Group D, P < 0.05; ¶Compared with the Group C, P < 0.05; ♠Compared with the Group D, P < 0.05; ▲Compared with the Group B, P < 0.05; A value of P < 0.05 was considered statistically significant.

Abbreviations: BMI, body mass index; CAT, COPD assessment test; CCQ, Clinical COPD Questionnaire; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist; LABA, long-acting β2-agonist; mMRC, modified Medical Research Council.

Characteristics of Pulmonary Function

As shown in Table 2, there were significant differences across Groups A to D in FEV1%, FVC%, FEV1/FVC, MEF25%, MEF75%, and PEF% (P < 0.001). Groups B and D had more severe airflow limitation than Groups A and C. In addition, the proportion of GOLD I–IV patients was significantly different across Groups A to D (P < 0.001). The proportion of GOLD I–II patients were higher in Group A, while GOLD III–IV patients were higher in Group D (P < 0.05).

Differences in Demographic and Clinical Characteristics for Different Severity of Airflow Limitation

In Group A, the proportions of patients in GOLD I–II and III–IV were 82.9% and 17.1%, respectively, and there were significant differences between GOLD I–II and III–IV in sex, schooling level, BMI, CAT, CCQ, treatments with LAMA and LAMA + LABA + ICS (P < 0.05). In Group B, the proportions of patients in GOLD I–II and III–IV were 48.3% and 51.7%, respectively, and there were significant differences in age, BMI, CAT, mMRC, CCQ, treatments with LAMA and LAMA + LABA + ICS (P < 0.05). The proportions of patients in GOLD I–II and III–IV were 63.9 and 36.1% in Group C and there were significant differences in BMI, CAT, mMRC, CCQ, treatments with LAMA and LAMA + LABA + ICS (P < 0.05). In Group D, the proportions of patients in GOLD I–II and III–IV were 36.1% and 63.9%, respectively, and there were significant differences in schooling level, BMI, CAT, mMRC, CCQ, treatments with LAMA and LAMA + LABA + ICS (P < 0.05) (Table 3).

Differences in Future Exacerbations and Mortality in Groups A, B, C and D After 18 Months of Follow-Up (N = 792)

After 18 months of follow-up, 792 patients were analyzed for future exacerbations. There were significant differences in exacerbations and hospitalizations rates among Groups A, B, C and D (P < 0.001). The numbers of frequent exacerbators in Groups A, B, C and D were 14 (10.5%), 43 (14.6%), 21 (20.4%) and 70 (26.8%), respectively, while the percentage mortalities were significantly different among the four groups (P < 0.01) at 0.8, 4.4, 2.9 and 8.4%, respectively. There were more frequent exacerbators and a higher mortality rate in group D (Table 4).

In Groups A, B, C and D, there were no significant differences in exacerbations or hospitalizations rates between GOLD I–II and III–IV patients after 18 months of follow-up. In addition, the proportion of patients with exacerbations or hospitalizations were not significantly

Table 2 Characteristics of Pulmonary Function in Different Groups (N = 993)

Variables	Group A (n = 170)	Group B (n = 360)	Group C (n = 122)	Group D (n = 341)	P value
FEV1% (Mean ± SD)	65.7 ± 18.4 *# &	49.7 ± 18.8 ¶	59.4 ± 22.2 ♠	45.7 ± 18.2 ▲	<0.001
FEV1/FVC (Mean ± SD)	54.5 ± 10.5 *# &	44.7 ± 12.5 ¶	50.6 ± 12.7 ♠	42.9 ± 11.8 ▲	<0.001
FVC% (Mean ± SD)	95.2 ± 17.3 * &	86.6 ± 17.4 ¶	91.3 ± 18.5 ♠	82.4 ± 18.8 ▲	<0.001
MEF25% (Mean ± SD)		21.9 ± 14.2	24.3 ± 14.9 ♠	20.6 ± 14.9	<0.001
MEF75% (Mean ± SD)	38.5 ± 23.5 *# &	22.9 ± 17.1 ¶	32.0 ± 21.9 ♠	19.2 ± 16.7 ▲	<0.001
PEF% (Mean ± SD)	62.1 ± 23.8 *# &	46.9 ± 18.8 ¶	54.4 ± 20.5 ♠	42.5 ± 19.4 ▲	<0.001
Bronchodilator test, n (%)					0.121
Positive	22 (12.9)	52 (14.4)	17 (13.9)	30 (8.8)	
Negative	148 (87.1)	308 (85.6)	105 (86.1)	311 (91.2)	
Severity of airflow limitation, n (%)					
I	37 (21.7) * &	26 (7.2) ¶	21 (17.2) ♠	18 (5.3)	<0.001
II	104 (61.2) *# &	148 (41.1)	57 (46.7) ♠	105 (30.8) ▲	<0.001
III	26 (15.3) *# &	130 (36.1)	33 (27.1) ♠	149 (43.7) ▲	<0.001
IV	3 (1.8) *# &	56 (15.6) ¶	11 (9.0) ♠	69 (20.2) ▲	<0.001

Notes: *Compared with the Group B, P < 0.05; #Compared with the Group C, P < 0.05; &Compared with the Group D, P < 0.05; ¶Compared with the Group C, P < 0.05; ♠Compared with the Group D, P < 0.05; ▲Compared with the Group B, P < 0.05; A value of P < 0.05 was considered statistically significant.
Abbreviations: FEV1, forced expiratory volume in one second; FVC, forced vital capacity; MEF, maximal expiratory flow; PEF, peak expiratory flow.

different in the same group with different severities of airflow limitation. The same trends could be seen in mortality rates and the proportion of frequent exacerbators in all groups (Table 5).

Discussion

In this study, we found that patients in Groups B and D were older. A similar result was observed in Oishi et al.[17] Smoking is a major environmental risk factor for COPD.[18] In this study, we found that Group D had more Ex-smokers and fewer current-smokers compared to Groups A, B and C. Liu et al[19] found the same results and patients with more symptoms are more likely to quit smoking. The number of female patients in this study was small. This may be because smoking is the main risk factor for COPD, and there are relatively few female patients who smoke in China.[20,21] Biofuel exposure is another risk factor for the development of COPD, which particularly affects females in developing countries.[22,23] Our research results also confirmed that Groups B, C and D had a higher biofuel exposure rate than Group A.

Since GOLD 2017 revised the assessment tool, the characteristics of airflow limitation in Groups A, B, C and D were unclear. In this study, the highest FEV1%, FVC%, FEV1/FVC, MEF25%, MEF75% and PEF% values were found in Group A, while the lowest in Group D. Lee et al[4] found the similar results, with FEV1% being highest in Group A and lowest in Group D. In addition, a study by Cui et al[24] also found that FEV1% and FEV1/FVC was the highest in Group A and lowest in Group D. GOLD I and II patients were concentrated in Groups A and C, while GOLD III and IV

Table 3 Differences in Demographic and Clinical Characteristics for Different Severity of Airflow Limitation in Groups A, B, C and D (N = 993)

	Group A (n = 170)		P value	Group B (n = 360)		P value	Group C (n = 122)		P value	Group D (n = 341)		P value
Variables	**GOLD**			**GOLD**			**GOLD**			**GOLD**		
	I–II (n = 141)	**III–IV (n = 29)**		**I–II (n = 174)**	**III–IV (n = 186)**		**I–II (n = 78)**	**III–IV (n = 44)**		**I–II (n = 123)**	**III–IV (n = 218)**	
Age (years)	61.0 ± 7.6	64.0 ± 8.8	0.059	66.4 ± 8.2	63.8 ± 7.9	0.003	62.9 ± 9.3	63.3 ± 8.8	0.844	66.7 ± 8.5	66.2 ± 7.7	0.108
Female, n (%)	21 (14.9)	0 (0)	0.027	25 (16.7)	15 (7.5)	0.057	7 (9.0)	2 (4.6)	0.486	20 (16.3)	22 (10.1)	0.096
Schooling level, n (%)			0.002			0.276			0.595			0.024
Primary school	45 (31.9)	14 (47.3)		80 (48.0)	68 (37.8)		36 (46.2)	20 (45.5)		71 (57.7)	89 (40.8)	
Junior high school	49 (34.8)	8 (27.6)		57 (33.3)	75 (40.4)		32 (41.0)	16 (36.4)		33 (26.8)	87 (39.9)	
High school	32 (22.7)	4 (13.8)		28 (13.3)	35 (17.9)		5 (6.4)	6 (13.6)		14 (11.4)	33 (15.2)	
University	15 (10.6)	3 (10.3)		9 (5.4)	8 (3.9)		5 (6.4)	2 (4.5)		5 (4.1)	9 (4.1)	
BMI (kg/m^2)	23.4 ± 3.5	21.7 ± 3.6	0.017	23.7 ± 3.5	21.8 ± 3.8	<0.001	23.0 ± 3.5	21.7 ± 3.1	0.034	23.0 ± 3.8	21.7 ± 3.5	0.006
Smoking history, n (%)			0.235			0.098			0.302			0.321
Never-smoker	28 (19.9)	2 (6.9)		35 (20.1)	30 (16.1)		15 (19.2)	4 (9.1)		27 (22.0)	42 (19.3)	
Ex-smoker	34 (24.1)	9 (31.0)		48 (27.6)	71 (38.2)		21 (26.9)	15 (34.1)		39 (31.7)	87 (39.9)	
Current-smoker	79 (56.0)	18 (62.1)		91 (52.3)	85 (45.7)		42 (53.9)	25 (56.8)		57 (46.3)	89 (40.8)	
Smoke (pack/year) (Median, IQR)	30 (36.5)	40 (30)	0.248	30 (30)	34.5 (40)	0.376	36.5 (40)	35.5 (40)	0.236	30 (30)	30 (32)	0.322
Biofuel exposure, n (%)			0.875			0.676			0.201			0.181
No	105 (74.5)	22 (75.9)		101 (59.3)	112 (59.0)		50 (64.1)	23 (52.3)		59 (48.0)	121 (55.5)	
Occupational exposure, n (%)			0.689			0.945			0.392			0.317
No	93 (66.0)	18 (62.1)		111 (64.7)	118 (62.2)		47 (60.3)	23 (52.3)		79 (64.3)	128 (58.7)	
CAT (Mean ± SD)	9.9 ± 4.7	12.5 ± 4.9	0.006	15.5 ± 4.8	17.7 ± 5.2	<0.001	12.9 ± 4.9	14.9 ± 5.2	0.034	17.6 ± 5.3	20.1 ± 5.9	<0.001
mMRC (Median, IQR)	1 (0)	1 (0)	0.814	2 (1)	3 (1)	<0.001	1 (0)	1 (0)	0.046	3 (1)	3 (1)	<0.001
CCQ (Mean ± SD)	15.2 ± 5.8	19.1 ± 5.3	0.001	21.6 ± 5.4	23.9 ± 5.8	<0.001	18.2 ± 4.9	21.1 ± 6.7	0.007	23.8 ± 5.6	26.4 ± 5.7	<0.001
Treatments, n(%)												
Any COPD medication	129 (91.5)	28 (96.6)	0.700	167 (96.0)	184 (98.7)	0.095	72 (90.3)	43 (97.7)	0.420	117 (95.1)	211 (96.8)	0.557

(*Continued*)

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Table 3 (Continued).

Variables		Group A (n = 170)		P value	Group B (n = 360)		P value	Group C (n = 122)		P value	Group D (n = 341)		P value
		GOLD			GOLD			GOLD			GOLD		
		I–II (n = 141)	III–IV (n = 29)		I–II (n = 174)	III–IV (n = 186)		I–II (n = 78)	III–IV (n = 44)		I–II (n = 123)	III–IV (n = 218)	
	LAMA	77 (54.6)	10 (34.5)	0.048	87 (48.0)	36 (17.3)	<0.001	49 (62.8)	11 (25.0)	<0.001	69 (56.1)	42 (19.3)	<0.001
	LABA+ICS	11 (7.8)	1 (3.5)	0.693	18 (11.3)	15 (10.3)	0.454	7 (9.0)	3 (6.8)	0.677	7 (5.7)	11 (5.0)	0.798
	LAMA+LABA	1 (0.7)	0	1.000	0	2 (1.1)	0.499	0	0	-	0	4 (1.8)	0.301
	LAMA+LABA+ICS	38 (26.9)	17 (58.6)	0.001	60 (35.3)	130 (69.9)	<0.001	14 (17.9)	29 (65.9)	<0.001	40 (32.5)	154 (70.6)	<0.001
Exacerbations in the past year (Mean ± SD)		0.1 ± 0.3	0.1 ± 0.4	0.964	0.1 ± 0.3	0.1 ± 0.3	0.930	2.3 ± 2.3	2.7 ± 2.9	0.427	3.4 ± 3.8	3.5 ± 4.2	0.820
Hospitalizations in the past year (Mean ± SD)		0	0	N/A	0	0	N/A	0.9 ± 1.1	1.0 ± 0.9	0.775	1.3 ± 1.4	1.4 ± 1.5	0.712

Note: A value of $P < 0.05$ was considered statistically significant.

Abbreviations: BMI, body mass index; CAT, COPD assessment test; CCQ, Clinical COPD Questionnaire; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist; LABA, long-acting β2-agonist; mMRC, modified Medical Research Council; N/A, not applicable.

patients were concentrated in Groups B and D. This is consistent with the results of Cabrera Lopez et al.[25] However, the proportion of GOLD IV patients in Groups A was relatively small. This was associated with less symptoms and a lower risk in Group A patients.

In the GOLD 2011 guidelines, GOLD classification of airflow limitation was used to guide combined COPD assessment. Briefly, GOLD I–II categories indicated low risk, while GOLD III–IV indicated high risk.[26] Therefore, we divided Groups A, B, C and D into two subgroups, one for GOLD I–II patients, and one for GOLD III–IV patients. The results showed that patients in GOLD III–IV had a lower BMI and proportion of LAMA, but higher CAT, CCQ and proportions of LAMA + LABA + ICS. This result implied that different severities of airflow limitation had an impact on symptom scores and treatments in the same groups.

Since GOLD 2017 removed pulmonary function, there has been no research on the future exacerbations in different groups of COPD patients. Therefore, we analyzed the future exacerbations and mortality in Groups A, B, C and D, and in the same groups with different severity of airflow limitation after 18 months of follow-up. The period of 18 months was chosen because one-year follow-up times did not reflect future exacerbations in COPD patients well.[27] The result showed that the exacerbations and hospitalizations rates were significantly different among different groups. The proportion of frequent exacerbators and mortality rates showed the same results. What' more, Group D had more exacerbations and hospitalizations rate, along with a higher mortality rate. However, it was noted that the mortality rate was relatively low in this study because the patients were only followed-up for 18 months. Furthermore, we conducted analysis of the different severity of airflow limitation subgroups in Groups A, B, C and D. The results were surprising, in that there were no differences in frequency of exacerbations or hospitalizations in all groups after 18 months of follow-up. Also, the mortality rates and proportions of frequent exacerbators were not significantly different. This result implied that GOLD classification of airflow limitation had no impact on the ABCD grouping in terms of future exacerbations and mortality. In other words, as described in the GOLD 2017 guidelines, combined COPD assessment should separate pulmonary function from the "ABCD" grouping.[9] However, Gedebjerg et al[28] found that the 16 subgroup (1A-4D) classification, combining GOLD grade

Table 4 Future Exacerbations and Mortality in Groups A, B, C and D After 18 Months of Follow-Up (N = 792)

Variables	Group A (n = 133)	Group B (n = 295)	Group C (n = 103)	Group D (n = 261)	P value
Exacerbations (Mean ± SD)	0.2 ± 0.5 &	0.3 ± 0.8	0.4 ± 0.7 ♠	0.8 ± 1.3 ▲	<0.001
Exacerbations, n (%)					<0.001
0	112 (84.2) * # &	222 (75.2)	72 (69.9) ♠	150 (57.5) ▲	
1	16 (12.0)	40 (13.6)	20 (19.4)	41 (15.7)	
≥ 2	4 (3.0) &	20 (6.8)	8 (7.8) ♠	48 (18.4) ▲	
Hospitalizations (Mean ± SD)	0.1 ± 0.4 &	0.2 ± 0.4	0.3 ± 0.6	0.3 ± 0.7 ▲	0.001
Hospitalizations, n (%)					0.001
0	119 (89.4) * # &	247 (83.7) ¶	80 (77.7) ♠	183 (70.1) ▲	
≥ 1	13 (9.8) * # &	35 (11.9) ¶	20 (19.4) ♠	56 (21.5) ▲	
Frequent Exacerbators, n (%)	14 (10.5) # &	43 (14.6) ¶	21 (20.4) ♠	70 (26.8) ▲	<0.001
Mortality, n (%)	1 (0.8) * # &	13 (4.4) ¶	3 (2.9) ♠	22 (8.4)	0.005

Notes: *Compared with the Group B, P < 0.05; #Compared with the Group C, P < 0.05; &Compared with the Group D, P < 0.05; ¶Compared with the Group C, P < 0.05; ♠Compared with the Group D, P < 0.05; ▲Compared with the Group B, P < 0.05; A value of P < 0.05 was considered statistically significant.

with the grouping according to GOLD 2017, increased the predictive ability for mortality, which is inconsistent with this study. It may be that our sample size is too small, with only a small number of patients dying during the 18 months of follow-up in this study. In addition, we have analyzed the data in this study to validate "16 subgroup (1A-4D) classification combining GOLD grade" and found that the mortality rates, exacerbations and hospitalizations rates show no differences (Supplement Tables 1 and 2).

This study still has some limitations. Firstly, the number of patients in Groups A and C was small. It may be that patients in Groups A and C have few symptoms, and typically in China, people attend hospital only once their symptoms are more severe. In addition, there were 201 patients lost to follow-up, which might have an impact on the results of the study. However, we analyzed the characteristics of these patients and found that there were no statistical differences when compared with the patients who remained in the study (Supplement Tables 3 and 4). Then, there was a low number of patients using dual bronchodilator LAMA + LABA, and a high rate of triple therapy was used in Group A. This may skew survival in a way that has not been accounted for. Finally, some of patients stop drugs treatment while most of patients of pharmacological regimens remained stable after 18 months of follow-up. However, we have analyzed the exacerbations and hospitalizations rates between the patients of pharmacological regimens remained stable and patients who stop drugs treatment in Groups A, B, C and D with different airflow limitation severity after 18 months of follow-up, and found that there were no significant differences (Supplement Tables 5 and 6).

Conclusions

In summary, our study revealed that there are significant differences in pulmonary function across Groups A to D, and that Groups B and D have more severe airflow limitation. Also, there are significant differences in exacerbations and mortality rates among different groups after 18 months of follow-up. However, in the GOLD groups with different severity of airflow limitation, the exacerbations, hospitalizations and mortality rates were no significant differences. In other words, GOLD classification of airflow limitation has no impact on future exacerbations and mortality rates in Groups A, B, C and D. It implies that pulmonary function is not a good indicator for predicting exacerbation.

Table 5 Future Exacerbations and Mortality for Different Severity of Airflow Limitation in Groups A, B, C and D After 18 Months of Follow-Up (N=792)

	Group A (n = 133)		P value	Group B (n = 295)		P value	Group C (n = 103)		P value	Group D (n = 261)		P value
Variables	**GOLD**			**GOLD**			**GOLD**			**GOLD**		
	I–II (n = 109)	**III–IV (n = 24)**		**I–II (n = 146)**	**III–IV (n = 149)**		**I–II (n = 63)**	**III–IV (n = 40)**		**I–II (n = 93)**	**III–IV (n = 168)**	
Exacerbations (Mean ± SD)	0.2 ± 0.5	0.2 ± 0.5	0.859	0.3 ± 0.7	0.3 ± 0.8	0.682	0.3 ± 0.6	0.5 ± 0.9	0.240	0.6 ± 1.2	0.8 ± 1.4	0.314
Exacerbations, n (%)			0.671			0.935			0.582			0.264
0	91 (83.5)	21 (87.5)		108 (74.0)	114 (76.5)		46 (73.0)	26 (65.0)		60 (64.5)	90 (53.6)	
1	14 (12.8)	2 (8.3)		20 (13.7)	20 (13.4)		11 (17.5)	9 (22.5)		16 (17.2)	25 (14.9)	
≥ 2	3 (2.8)	1 (4.2)		9 (6.1)	11 (7.4)		4 (6.3)	4 (10.0)		13 (14.0)	35 (20.8)	
Hospitalizations (Mean ± SD)	0.1 ± 0.4	0.04 ± 0.2	0.121	0.2 ± 0.4	0.2 ± 0.5	0.910	0.2 ± 0.4	0.3 ± 0.8	0.332	0.3 ± 0.8	0.3 ± 0.7	0.956
Hospitalizations, n (%)			0.461			0.719			0.539			0.367
0	96 (88.0)	23 (95.8)		119 (81.5)	128 (85.9)		50 (82.0)	30 (75.0)		71 (76.3)	112 (66.7)	
≥ 1	12 (11.1)	1 (4.2)		18 (12.3)	17 (11.4)		11 (18.0)	9 (22.5)		18 (19.4)	38 (22.6)	
Frequent exacerbator, n (%)	13 (11.9)	1 (4.2)	0.464	21 (14.4)	22 (14.8)	0.926	12 (19.1)	9 (22.5)	0.672	23 (24.7)	47 (28.0)	0.571
Mortality, n (%)	1 (0.9)	0 (0)	1.000	9 (6.2)	4 (2.7)	0.145	2 (3.2)	1 (2.5)	1.000	4 (4.3)	18 (10.7)	0.074

Note: A value of $P < 0.05$ was considered statistically significant.
Abbreviation: GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Abbreviations

BMI, body mass index; COPD, chronic obstructive pulmonary disease; CAT, COPD assessment test; CCQ, Clinical COPD Questionnaire; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist; LABA, long-acting β2-agonist; MEF, maximal expiratory flow; mMRC, modified Medical Research Council; PEF, peak expiratory flow.

Data Sharing Statement

All publications discussed in the manuscript are available from the corresponding author on request.

Statement of Ethics

This study was registered in the Chinese Clinical Trial Registry (Registration number: ChiCTR-POC-17010431). This study was approved by an institutional review board from the Second Xiangya Hospital of Central South University and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent in this study.

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Author Contributions

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

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Disclosure

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