

Disease Burden and Unmet Needs in Chinese Patients with Symptomatic and Exacerbating COPD While on Triple Inhaled Therapy: A Cross-Sectional Real-World Study

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Background: Chronic obstructive pulmonary disease (COPD) is a common respiratory disease and a major cause of mortality and morbidity in China. Global studies have revealed a subgroup of patients who had COPD symptoms and frequent exacerbations while receiving triple inhaled therapy. This study aimed to describe the clinical characteristics and disease burden of this patient population in China.

Methods: This cross-sectional, real-world study drew data from the Adelphi COPD Disease Specific Programme (DSP)TM from July to November 2022 in China. Adult patients with a diagnosis of COPD and receiving triple therapy at survey date were included; among them, patients who had frequent productive cough and sputum, a history of smoking, ≥ 2 moderate or ≥ 1 severe exacerbation(s) in the prior 12 months and were receiving triple therapy were identified as the symptomatic SET cohort; all other patients were categorized as the triple therapy cohort. Disease-related characteristics and perceptions of disease control were described for both cohorts.

Results: Of the 135 patients receiving triple therapy, 39 (28.9%) were categorized into the symptomatic SET cohort and 96 (71.1%) into the triple therapy cohort. In the triple therapy and symptomatic SET cohorts, mean (SD) age was 65.9 (9.0) and 69.2 (8.7), respectively; mean (SD) number of exacerbations during the last 12 months was 1.3 (1.4) and 2.3 (1.3), respectively; mean (SD) CAT score was 21.0 (8.3) and 25.7 (7.1), respectively. According to physicians' perception, around 70% of patients in the symptomatic SET cohort had, at the minimum, somewhat controlled COPD (completely controlled: 2.6%; well controlled: 28.2%; somewhat controlled: 38.5%). Satisfactory COPD control was achieved in 33.3% and 38.5% of patients in the symptomatic SET cohort as perceived by physicians and patients, respectively.

Conclusion: Substantial disease burden and large unmet needs existed among patients with symptomatic and exacerbating COPD while receiving triple inhaled therapy in clinical settings in China. Novel therapeutic options and improved guideline-directed disease management are needed.

Keywords: exacerbations, triple inhaled therapy, physician survey, patient-reported outcomes, disease burden, China

Introduction

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease and a major cause of mortality and morbidity.^{1,2} In China, the prevalence of COPD was 8.6% among adults aged 20 years or older in 2018, corresponding to nearly 100 million patients,³ and representing approximately 25% of all COPD cases globally.⁴ As of 2017, COPD ranked as the third leading cause of both death and disease burden measured by disability-adjusted life years in China.⁵ Common COPD symptoms include chronic dyspnea, cough and expectoration,⁶ an acute worsening of these symptoms defines an exacerbation and results in the need for additional therapy.⁷ Chinese patients with COPD are substantially impacted by exacerbations,⁸

which severely affect patients' health status,⁹ and represent a major risk factor for mortality, poor health-related quality of life (HRQoL), frequent hospital admission and increased healthcare resource utilization (HCRU).⁹

Inhaled therapy is the cornerstone of COPD treatment, including bronchodilation with inhaled long-acting β_2 -agonists (LABA) and/or long-acting muscarinic antagonists (LAMA).⁷ Inhaled corticosteroids (ICS) are further added for patients with recurrent exacerbations to form triple therapy, the highest level of inhaled treatment for COPD.⁷ Global evidence has suggested that, while receiving the maximal triple inhaled therapy, some patients still experienced frequent exacerbations.^{10–12} For instance, an observational study from the UK reported that 14.8% of patients experienced frequent exacerbations despite receiving at least three months of maximal triple inhaled therapy.¹¹ These patients presented with significantly higher risks of COPD-related death compared to the overall patients with maintenance-treated COPD, representing heavy disease burden and unmet need.¹¹ Ongoing research into potential new treatment options for such patients includes randomized clinical trials (RCTs) evaluating biologics with inflammatory targets, such as anti-IL-5, anti-IL-5R α , anti-IL-4R α , anti-thymic stromal lymphopoietin (TSLP) and anti-IL-33.^{13,14}

Although several studies have reported on the real-world effectiveness of triple therapy in Chinese patients with COPD,^{15,16} few have focused on patients who experienced symptoms and frequent exacerbations while on triple therapy, and little is known about the disease burden of these patients. A previous global study has revealed substantial clinical burden and extensive unmet needs in patients with COPD who experienced frequent symptoms and exacerbations while receiving triple inhaled therapy;¹⁷ here in the current study, we aimed to understand the disease burden and unmet needs in such patient population in China.

Methods

Study Design and Participants

This observational, real-world study utilized data from the Adelphi Real World COPD Disease Specific Programme (DSP)TM. The Adelphi Real World DSPs are impartial data sources independent of any specific study and are not intended for addressing any prespecified research questions or hypotheses. The DSP methodology has been validated and used in previously published studies.^{18–21} The Adelphi Real World COPD DSP was a cross-sectional linked physician- and patient- survey conducted in nine countries (France, Germany, Italy, Spain, UK, US, Canada, Japan and China) and has been used in the previous global study.¹⁷ DSP data collected in China from July to November 2022 were drawn and analyzed for the current study.

The eligibility of physicians and patients in the DSP has been described previously.¹⁷ Physicians meeting the following criteria were eligible for inclusion: hospital-based health care professionals (HCP), including primary care physicians (PCP) and respiratory specialists; personally responsible for managing patients with COPD; and attended to three or more patients with COPD in a typical month. There were no exclusion criteria for physicians. Patients meeting the following criteria were eligible for inclusion: aged 18 years or older; with a physician-confirmed diagnosis of COPD; and were not concurrently involved in a clinical trial at the time of data collection. Patients were excluded if they were younger than 18 years of age or if they were currently enrolled in a clinical trial. Each participating physician completed patient record forms for up to five consecutive eligible patients consulting for routine care. These patients were then invited to independently complete a voluntary patient self-completion survey and constituted the overall DSP population. From the overall DSP population, patients who were receiving triple therapy for COPD treatment were selected, among which a symptomatic SET cohort was established by identifying patients who had been reported by their physicians as having frequent productive cough and sputum in the four weeks preceding survey date and met the following criteria: 1) history of smoking (current or former smokers); 2) ≥ 2 moderate (defined as requiring treatment with antibiotic and/or oral corticosteroid without emergency room visit or overnight hospitalization) or ≥ 1 severe (defined as requiring emergency room visit or overnight hospitalization) exacerbation in the 12 months preceding the survey date; and 3) a prescription for triple inhaled therapy at the time of survey.¹⁷ All other patients receiving triple therapy (excluding patients in the symptomatic SET cohort) were categorized into the triple therapy cohort.

Ethics

Informed consent was obtained from all participating patients via a tick box in the patient self-completion survey. Data were deidentified and pseudo-anonymized to ensure confidentiality and were aggregated before sharing with the subscriber and/or for publication.

This study was submitted to the Pearl Institutional Review Board (protocol number: #22-ADRW-147). Ethics approval was waived as this was a healthcare market research survey and data collection were in line with European Pharmaceutical Marketing Research Association guidelines.²² Each survey was performed in full accordance with relevant legislation at the time of data collection, including the US Health Insurance Portability and Accountability Act 1996.²³

Measures

Data forms completed by physicians and patients were linked via a unique, pseudo-anonymized number. All information was recorded on the survey completion date from available medical records or designated recall periods for physicians and patients, with no follow-up data collected.

Physicians reported the level of disease burden and unmet needs including respiratory symptoms; exacerbation patterns; the level of COPD control based on physicians' perception; their satisfaction with the current COPD control and whether they believed the best possible control was achieved; their perception of COPD severity (at initiation of current treatment and at the time of survey); and impact of COPD on daily lives. Additionally, physicians reported patients' characteristics including demographics, comorbidities, asthma diagnosis, COPD-related characteristics and current treatment regimens. COPD-related characteristics included most recent blood eosinophil counts (BEC), lung function measured by post-bronchodilator (post-BD) forced expiratory volume in one second (FEV₁) as a percentage of the predicted value (FEV₁ [% predicted]), and Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification. Physicians also reported HCP involvement in the management of patients with COPD.

Patients self-reported the level of COPD control and impact of COPD on their daily lives using validated patient-reported outcome measures (PROMs), including the COPD Assessment Test (CAT; scores ranging from 0 to 40, with higher scores reflecting greater symptom severity), the European Quality of Life-5 Dimension-5 Level (EQ-5D-5L; Chinese-specific tariff; scores ranging from 0 to 1, with 0 representing worst imaginable health state and 1 representing best imaginable health state), the European Quality of Life-Visual Analogue Scale (EQ-VAS; scores ranging from 0 to 100, reflecting the worst to best imaginable health state), and work productivity and activity impairment (WPAI; four separate scores each ranging from 0 to 100, representing the percentage of work time missed or percentage impairment). Patients also reported their satisfaction with COPD control and their perception of disease control.

Data Analysis

Data were described using mean (standard deviation [SD]) or median (quartile [Q]1, Q3) for continuous variables and frequencies or percentages for categorical variables. Although this study was designed as a descriptive study, an exploratory bivariate analysis was performed to compare the outcomes between the two cohorts. Numerical variables were analyzed using Student's *t*-test, categorical variables were analyzed using Fisher's Exact test (Chi-squared test as an alternative when Fisher's Exact could not be calculated) and ordered categorical variables were analyzed using Mann-Whitney U (non-parametric) test. A significance level of $\alpha = 0.05$ was used, and all tests were two-sided. Missing data were handled as missing with no imputation performed. All analyses were conducted using Stata 19 (StataCorp. 2025. Stata Statistical Software: Release 19. College Station, TX, USA: StataCorp LLC).

Results

Patient Demographics and Clinical Characteristics

A total of 236 HCPs participated in the DSP and provided information on 844 patients with COPD. Among them, 135 patients received triple therapy for COPD treatment and were included in the current study, including 39 (28.9%) patients in the symptomatic SET cohort and 96 (71.1%) patients in the triple therapy cohort.

Patients in the triple therapy cohort had a mean (SD) age of 65.9 (9.0) years, with 61.5% being male. Patients in the symptomatic SET cohort had a mean (SD) age of 69.2 (8.7) years, with 94.9% being male. Former smokers were more prevalent in symptomatic SET cohort (triple therapy: 48.9%; symptomatic SET: 71.8%; p value <0.001). Hypertension was the most common cardiovascular comorbidity (triple therapy: 40.6%; symptomatic SET: 48.7%); diabetes without complications was found in 13.5% of patients in the triple therapy cohort and 25.6% of patients in the symptomatic SET cohort; diabetes with complications was found in 6.3% and 5.1% of patients in the two cohorts, respectively. Asthma-associated characteristics were present in 19.8% and 18.0% of patients in the triple therapy and symptomatic SET cohort, respectively. Results of BEC were available for 39 patients in the triple therapy cohort and 18 patients in the symptomatic SET cohort, of whom 23.1% in the triple therapy cohort and 27.8% in the symptomatic SET cohort had BEC ≥ 300 cells/ μL ($p = 0.777$) (Table 1).

Table 1 Demographics and Clinical Characteristics

	Triple Therapy n=96	Symptomatic SET n=39	p Value ^a
Age, years, mean (SD)	65.9 (9.0)	69.2 (8.7)	0.049
Sex, male, n (%)	59 (61.5)	37 (94.9)	<0.001
BMI, kg/m ² , mean (SD)	23.6 (2.8)	23.4 (2.8)	0.741
Smoking status			
Patients with missing data, n	2	0	
Patients included, n	94	39	<0.001
Current smoker, n (%)	14 (14.9)	11 (28.2)	
Former smoker, n (%)	46 (48.9)	28 (71.8)	
Never smoked, n (%)	34 (36.2)	/	
Cardiovascular comorbidities ^b , n (%)			
Hypertension	39 (40.6)	19 (48.7)	0.389
Cerebrovascular disease	8 (8.3)	10 (25.6)	0.007
Elevated cholesterol/hyperlipidemia	8 (8.3)	7 (17.9)	0.133
Coronary artery disease	6 (6.3)	6 (15.4)	0.104
Cardiac arrhythmias	6 (6.3)	4 (10.3)	0.474
Congestive heart failure	2 (2.1)	1 (2.6)	1.000
Myocardial infarction	1 (1.0)	1 (2.6)	0.496
Others	0	1 (2.6)	0.289
Non-cardiovascular comorbidities, n (%)			
Diabetes without complications	13 (13.5)	10 (25.6)	0.090
Diabetes with complications	6 (6.3)	2 (5.1)	1.000
Osteoporosis	2 (2.1)	6 (15.4)	0.007
Allergic Rhinitis	19 (19.8)	5 (12.8)	0.337
Pulmonary arterial hypertension	2 (2.1)	5 (12.8)	0.021
Chronic rhinosinusitis	8 (8.3)	2 (5.1)	0.723
Having characteristics associated with asthma, n (%)	19 (19.8)	7 (17.9)	0.806
Most recent BEC, cells/ μL			
Patients with missing data, n	57	21	
Patients included, n	39	18	
Mean (SD)	342.8 (620.9)	310.7 (294.0)	0.836
Median (Q1, Q3)	213.0 (180.0, 296.0)	192.0 (150.0, 487.0)	
<150 cells/ μL , n (%)	9 (23.1)	4 (22.2)	0.777
150–299 cells/ μL , n (%)	21 (53.9)	9 (50.0)	
≥ 300 cells/ μL , n (%)	9 (23.1)	5 (27.8)	

(Continued)

Table 1 (Continued).

	Triple Therapy n=96	Symptomatic SET n=39	p Value ^a
Most recent post-BD FEV ₁ (% predicted) ^c			
Patients with missing data, n	45	15	
Patients included, n	51	24	
Mean (SD)	59.6 (15.8)	46.2 (15.8)	0.001
Median (Q1, Q3)	60.0 (48.0, 68.0)	46.0 (32.0, 60.5)	
Post-BD FEV ₁ , n (%)			0.003
≥80% (mild)	7 (13.7)	1	
50%–79% (moderate)	29 (56.9)	10 (41.7)	
30%–49% (severe)	14 (27.5)	9 (37.5)	
<30% (very severe)	1 (2.0)	5 (20.8)	
Physician perceived severity at treatment initiation, n (%)			
Patients with missing data, n	0	1	
Patients included, n	96	38	
Mild	16 (16.7)	1 (2.6)	0.009
Moderate	47 (49.0)	16 (42.1)	
Severe	33 (34.4)	21 (55.3)	
Physician perceived severity on survey date, n (%)			0.007
Mild	17 (17.7)	1 (2.6)	
Moderate	45 (46.9)	16 (41.0)	
Severe	34 (35.4)	22 (56.4)	
GOLD severity of airflow limitation classification, n (%) ^d			
Patients with missing data, n	1	0	
Patients included, n	95	39	
GOLD 1 (FEV ₁ ≥80% predicted)	13 (13.7)	0	0.045
GOLD 2 (FEV ₁ 50%–79% predicted)	29 (30.5)	12 (30.8)	
GOLD 3 (FEV ₁ 30%–49% predicted)	36 (37.9)	16 (41.0)	
GOLD 4 (FEV ₁ <30% predicted)	17 (17.9)	11 (28.2)	
Current treatment			
Triple therapy regimens, n (%)			0.080
ICS/LABA/LAMA	54 (56.3)	29 (74.4)	
ICS/LABA + LAMA	40 (41.7)	9 (23.1)	
ICS + LABA/LAMA	2 (2.1)	1 (2.6)	
Treatment duration of triple therapy, weeks, mean (SD)	27.1 (38.4)	19.3 (22.9)	0.238
Patients receiving traditional Chinese medicine, n (%)			
Patients with missing data, n	9	5	
Patients included, n	87	34	
Yes	22 (25.3)	9 (26.5)	0.893
No	65 (74.7)	25 (73.5)	

Notes: ^aStatistical analyses were conducted using Student's *t*-tests, Fisher's Exact tests, Mann–Whitney *U*-tests and Pearson's Chi-Squared tests as appropriate ($p < 0.05$ indicated in bold). ^bAll cardiovascular comorbidities in the symptomatic SET cohort were listed; in the triple therapy cohort, additional cardiovascular comorbidities included angina pectoris ($n=5$, 5.2%, $p = 0.321$), thrombosis ($n=1$, 1.0%, p value=1.000) and peripheral vascular disease ($n=1$, 1.0%, $p = 1.000$). ^cTaken from the patient's most recent post-BD FEV₁ (% predicted) test. ^dBased on physician-perceived severity of airflow limitation.

Abbreviations: BD, bronchodilator; BEC, blood eosinophil count; BMI, body mass index; FEV₁, forced expiratory volume in one second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; Q, quartile; SD, standard deviation; SET, smoking, exacerbating and on triple therapy.

Among the patients with lung function results available (triple therapy: $n=51$; symptomatic SET: $n=24$), median post-BD FEV₁ (% predicted) was 60.0% in the triple therapy cohort and 46.0% in the symptomatic SET cohort ($p = 0.001$). In the triple therapy cohort, the percentages of patients with physician-perceived mild, moderate and severe COPD were 16.7%, 49.0% and 34.4%, respectively, at the time of current COPD treatment initiation and 17.7%, 46.9% and 35.4%,

respectively, at the time of the survey date. In the symptomatic SET cohort, the percentages of physician-perceived mild, moderate and severe COPD were 2.6%, 42.1% and 55.3%, respectively, at the time of current COPD treatment initiation and 2.6%, 41.0% and 56.4%, respectively, at the time of the survey date. GOLD severity of airflow limitation (GOLD 1–4) based on physicians' perception for both cohorts are also summarized in [Table 1](#).

Fixed-dose ICS/LABA/LAMA was the most common regimen and was used in 56.3% of patients in the triple therapy cohort and 74.4% in the symptomatic SET cohort, followed by ICS/LABA plus a LAMA (triple therapy: 41.7%; symptomatic SET: 23.1%) and ICS plus LABA/LAMA (triple therapy: 2.1%; symptomatic SET: 2.6%). Mean (SD) duration of current triple therapy regimen was 27.1 (38.4) weeks for the triple therapy cohort and 19.3 (22.9) weeks for the symptomatic SET cohort. Additionally, traditional Chinese medicine was used in 25.3% and 26.5% of patients in the triple therapy and the symptomatic SET cohorts, respectively ([Table 1](#)). No significant differences between the two cohorts regarding the above treatment were observed ($p \geq 0.05$).

COPD Symptoms Reported by Physicians and Exacerbations

According to physicians' reports, the most frequent respiratory symptoms during the last four weeks prior to survey date and the most troublesome symptoms for both the triple therapy and the symptomatic SET cohorts are shown in [Figure 1A](#) and [B](#). Wheezing (55.8%), shortness of breath during exertion/exercise (55.8%) and dry cough (44.2%) were the most frequently reported symptoms in the triple therapy cohort. In the symptomatic SET cohort, aside from productive cough/sputum (100%), wheezing (74.4%) and a tight feeling in the chest (51.3%) were the most frequently reported symptoms. Shortness of breath during exertion/exercise (19.2%) was reported as the most troublesome symptom in the triple therapy cohort and wheezing (43.6%) was reported as the most troublesome symptom in the symptomatic SET cohort. As shown in [Figure 1C](#), 29.0% of patients in the symptomatic SET cohort and 7.7% of patients in the triple therapy cohort were reported to experience COPD symptoms every day during daytime hours ($p < 0.001$); symptom frequency was significantly higher in the symptomatic SET cohort compared to triple therapy cohort regardless of different observational period ($p < 0.05$ for all).

[Table 2](#) summarizes key aspects of the patients' exacerbation profiles during the last 12 months. In the triple therapy cohort, mean (SD) number of exacerbations in the last 12 months was 1.3 (1.4) and 35.4% of patients were free of exacerbation. In the symptomatic SET cohort, mean (SD) number of exacerbations during the last 12 months was 2.3 (1.3), with 30.8%, 33.3%, 17.9% and 17.9% of patients experiencing an exacerbation once, twice, three times and four or more times, respectively. The exacerbation profile was significantly different between the two cohorts ($p < 0.001$). Changes in weather/climate were considered the most common exacerbation trigger for both cohorts. Physicians perceived that the significantly higher proportion of patients in the symptomatic SET cohort (87.2%) had high future exacerbation risks compared with patients in the triple therapy cohort (58.3%) ($p = 0.001$).

COPD Control Status

According to physicians' perception, 2.6%, 28.2% and 38.5% of patients had completely controlled, well controlled and somewhat controlled COPD in the symptomatic SET cohort, respectively, while the corresponding percentages were 7.3%, 50.0% and 27.1% in the triple therapy cohort. The proportions of patients perceived by physicians as having poorly controlled and uncontrolled COPD were 28.2% and 2.6%, respectively, in symptomatic SET cohort, and 13.5% and 2.1%, respectively, in the triple therapy cohort ([Figure 2A](#)). The physician perceived COPD control between the two cohorts was significantly different ($p = 0.005$).

Physicians' and patients' satisfaction with the level of COPD control are reported for both cohorts in [Figure 2B](#). Physicians and patients were more unsatisfied with COPD control in the symptomatic SET cohort compared to the triple therapy cohort. For instance, physicians were not satisfied with the level of COPD control and believed that better control could be achieved for 25.6% of patients in the symptomatic SET cohort and 17.8% of patients in the triple therapy cohort; and physicians were not satisfied but believed that the best possible control was achieved for 41.0% of patients in the symptomatic SET cohort and 27.4% of patients in the triple therapy cohort ($p = 0.001$). Patients' satisfaction with COPD control showed a similar pattern with those of physicians and there was significant difference between the two cohorts ($p = 0.010$).



Figure 1 Respiratory symptoms reported by physicians for the patients in the triple therapy cohort and patients in the symptomatic SET cohort. **(A)** Frequently reported symptoms during the last four weeks prior to survey date; n=95 for triple therapy cohort and n=39 for symptomatic SET cohort. **(B)** Most troublesome symptoms; n=94 for triple therapy cohort and n=39 for symptomatic SET cohort. **(C)** Symptom frequency; immediately on awakening: n=91 for triple therapy cohort and n=37 for symptomatic SET cohort; during the rest of the day: n=91 for triple therapy cohort and n=38 for symptomatic SET cohort; during the evening: n=90 for triple therapy cohort and n=36 for symptomatic SET cohort; overnight: n=90 for triple therapy cohort and n=39 for symptomatic SET cohort. ^aStatistical analyses were conducted using Fisher's Exact tests, Mann-Whitney U-tests and Pearson's Chi-Squared tests as appropriate ($p < 0.05$ indicated in bold).

Abbreviation: SET, smoking, exacerbating and on triple therapy.

Table 2 COPD Exacerbations

	Triple Therapy n=96	Symptomatic SET n=39	p Value ^a
Number of exacerbations during the last 12 months			
Mean (SD)	1.3 (1.4)	2.3 (1.3)	<0.001
Median (Q1, Q3)	1.0 (0, 2.0)	2.0 (1.0, 3.0)	
Number of exacerbations, n (%)			<0.001
0	34 (35.4)	/	
1	32 (33.3)	12 (30.8)	
2	11 (11.5)	13 (33.3)	
3	6 (6.3)	7 (17.9)	
4 or more	13 (13.5)	7 (17.9)	
Most common exacerbation triggers ^b			
Patients with missing data, n	12	1	
Patients included, n	84	38	
Changes in weather/climate, n (%)	38 (45.2)	24 (63.2)	0.067
Viral infection, n (%)	26 (31.0)	20 (52.6)	0.022
Cold weather/air, n (%)	33 (39.3)	18 (47.4)	0.402
Bacterial infection, n (%)	21 (25.0)	15 (39.5)	0.105
Outdoor pollution, n (%)	29 (34.5)	14 (36.8)	0.804
Physician-perceived future exacerbation risk, n (%)			0.001
High	56 (58.3)	34 (87.2)	
Low	40 (41.7)	5 (12.8)	

Notes: ^aStatistical analyses were conducted using Student's t-tests, Fisher's Exact tests, Mann-Whitney U-tests and Pearson's Chi-Squared tests as appropriate ($p < 0.05$ indicated in bold). ^bThe five most frequently reported exacerbation triggers for patients in the symptomatic SET cohort were listed.

Abbreviations: Q, quartile; SD, standard deviation; SET, smoking, exacerbating and on triple therapy.

Impact of COPD on Daily Lives and HRQoL

Physician-reported impact of COPD on patients' daily lives is shown in [Figure 3](#). Large proportions of patients in the symptomatic SET cohort frequently or constantly experienced impacts of COPD on their daily lives compared to patients in the triple therapy cohort; exercise, mood and sleep were the most frequently impacted domains.

Patient-reported outcomes of HRQoL (CAT, EQ-5D-VAS, EQ-5D-5L and WPAI scores) in the triple therapy and symptomatic SET cohorts are summarized in [Table 3](#). Among patients with data available (triple therapy: n=95; symptomatic SET: n=39), mean (SD) CAT score was 25.7 (7.1) in the symptomatic SET cohort and 21.0 (8.3) in the triple therapy cohort. For the CAT cough domain, 94.9% of patients in the symptomatic SET cohort and 93.7% of patients in the triple therapy cohort reported a score ≥ 2 . For the CAT phlegm/sputum domain, 92.3% in the symptomatic SET cohort and 82.1% of patients in the triple therapy cohort reported a score ≥ 2 . Mean (SD) EQ-5D-VAS and EQ-5D-5L scores were 57.1 (15.8) and 0.6 (0.3), respectively, in the symptomatic SET cohort, and 61.9 (17.0) and 0.7 (0.2) in the triple therapy cohort. Among the limited patients with WPAI data available, work impact was notably severe in patients in the symptomatic SET cohort.

Physician Involvement and HCRU

Mean (SD) number of patient visits to HCPs during the last 12 months was 6.5 (3.6) in the triple therapy cohort and 7.1 (3.8) in the symptomatic SET cohort. In both cohorts, respiratory specialists were the most common HCPs visited by patients for initial consultation, diagnosis of COPD, maintenance treatment initiation and current treatment decision ([Table 4](#)).

Tertiary hospitals were the most frequently visited hospitals for both the triple therapy (65.6%) and symptomatic SET (71.8%) cohorts, followed by secondary hospitals (triple therapy: 29.2%; symptomatic SET: 23.1%) and community health centers (CHCs, triple therapy: 5.2%; symptomatic SET: 5.1%). In the triple therapy cohort (n = 96), 45 (46.9%)

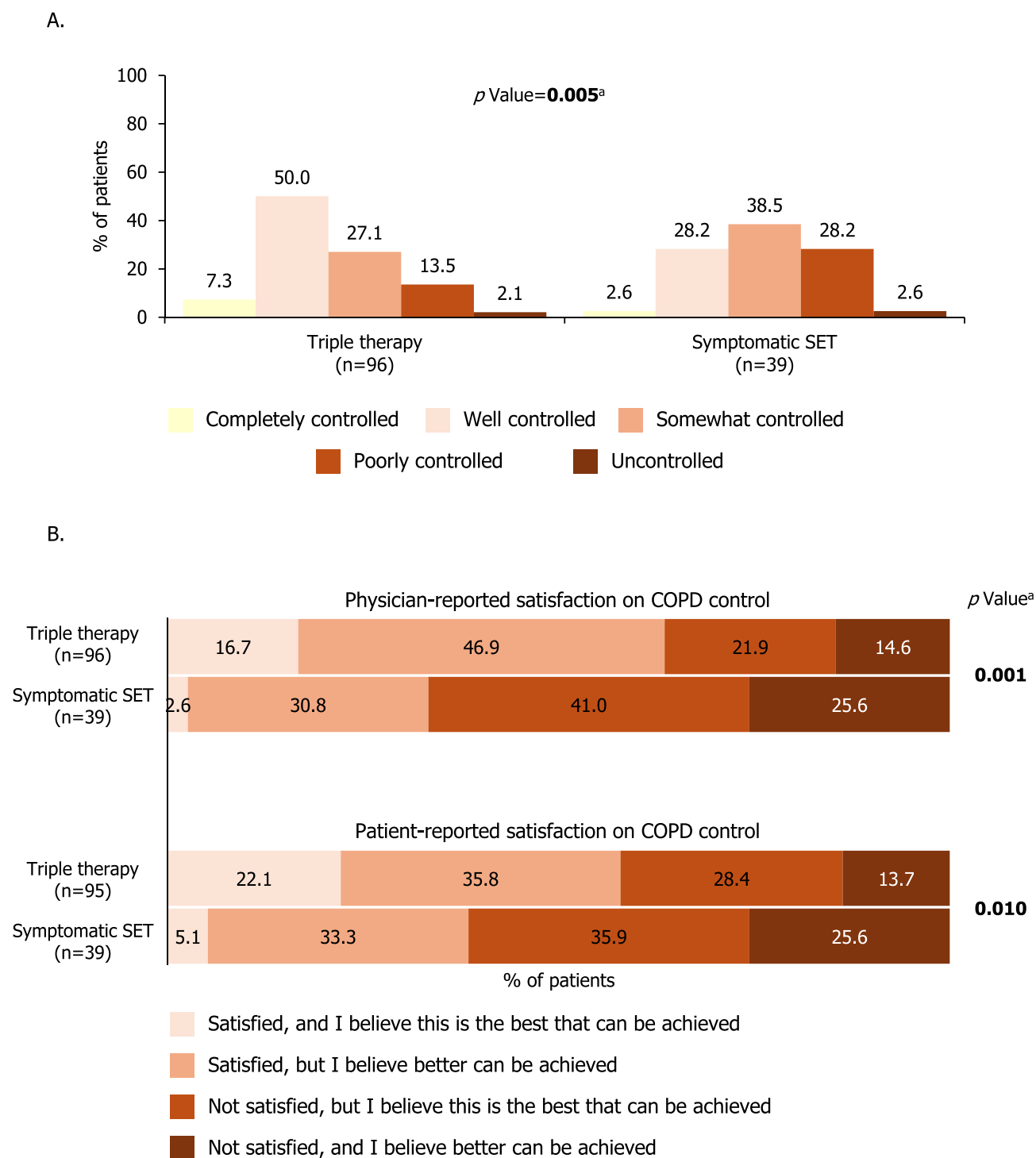


Figure 2 Physician perceived COPD control and physician- and patient-reported satisfaction with COPD control. **(A)** Physician perceived COPD control during the last four weeks prior to survey date. **(B)** Physician- and patient-reported satisfaction on COPD control. ^aStatistical analyses were conducted using Mann–Whitney *U*-tests ($p < 0.05$ indicated in bold).

Abbreviations: COPD, chronic obstructive pulmonary disease; SET, smoking, exacerbating and on triple therapy.

patients required hospital stays and 16 (16.7%) patients required intensive care unit (ICU) stays as a result of COPD exacerbations during the last 12 months; mean (SD) numbers of nights spent in hospital and ICU due to exacerbations were 5.0 (4.7) and 1.9 (2.3), respectively. In the symptomatic SET cohort ($n = 39$), 32 (82.1%) and 8 (20.5%) patients

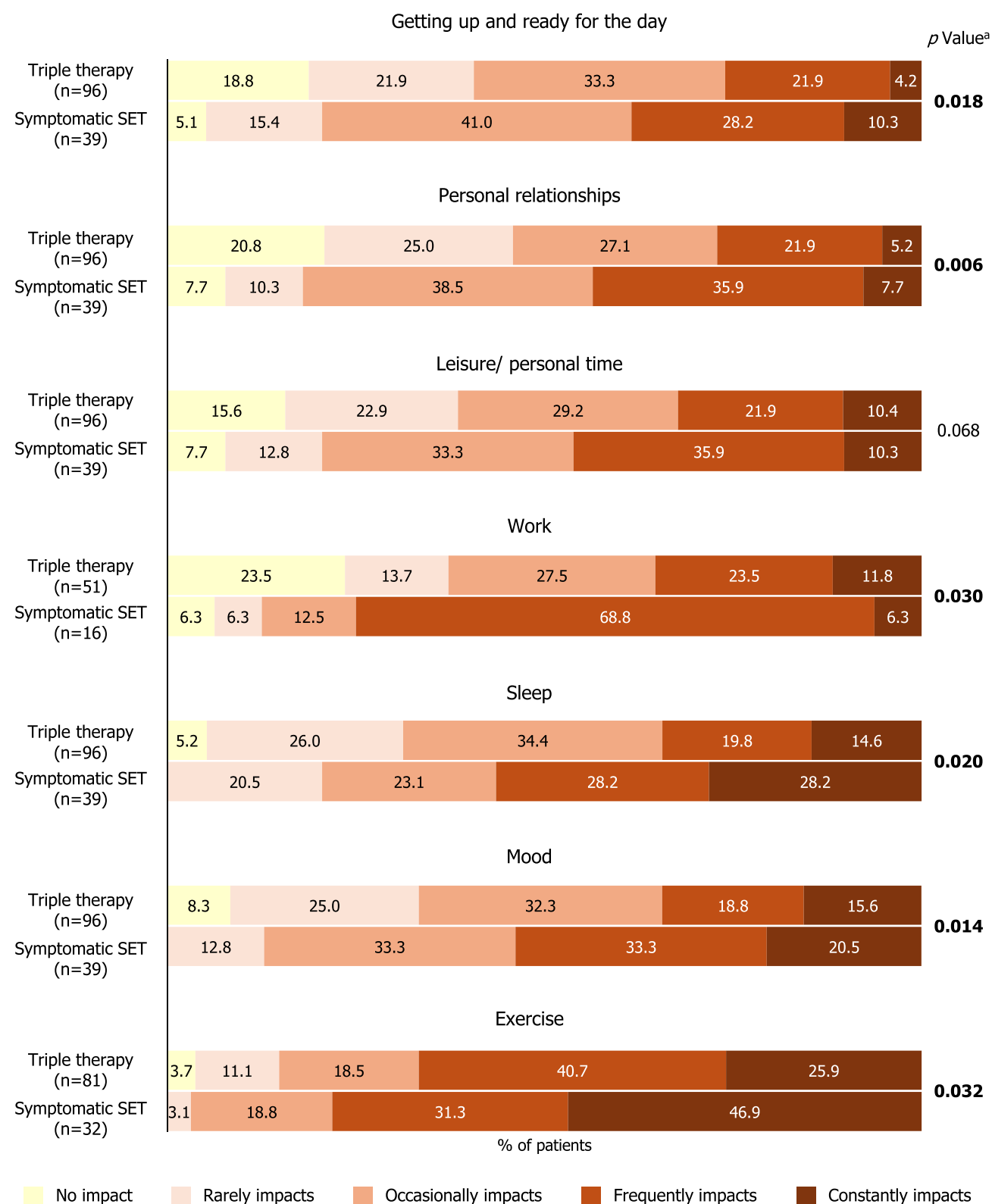


Figure 3 Impact of COPD on daily lives during the last four weeks. ^aStatistical analyses were conducted using Mann–Whitney U-tests ($p < 0.05$ indicated in bold).
Abbreviations: COPD, chronic obstructive pulmonary disease; SET, smoking, exacerbating and on triple therapy.

Table 3 Patient-Reported HRQoL

	Triple Therapy n=96	Symptomatic SET n=39	p Value ^a
CAT total score ^b			
Patients with missing data, n	1	0	
Patients included, n	95	39	
Mean (SD)	21.0 (8.3)	25.7 (7.1)	0.002
Median (Q1, Q3)	19.0 (14.0, 28.0)	27.0 (21.0, 31.0)	
<10, n (%)	5 (5.3)	/	0.321
≥10, n (%)	90 (94.7)	39 (100)	
CAT cough domain score, n (%) ^c			
Patients with missing data, n	1	0	
Patients included, n	95	39	
<2	6 (6.3)	2 (5.1)	1.000
≥2	89 (93.7)	37 (94.9)	
CAT phlegm/sputum domain score, n (%) ^d			
Patients with missing data, n	1	0	
Patients included, n	95	39	
<2	17 (17.9)	3 (7.7)	0.132
≥2	78 (82.1)	36 (92.3)	
EQ-5D-VAS ^e			
Patients with missing data, n	1	0	
Patients included, n	95	39	
Mean (SD)	61.9 (17.0)	57.1 (15.8)	0.133
Median (Q1, Q3)	64.0 (51.0, 75.0)	59.0 (50.0, 69.0)	
EQ-5D-5L (Chinese-specific tariff) ^f			
Patients with missing data, n	1	0	
Patients included, n	95	39	
Mean (SD)	0.74 (0.19)	0.62 (0.26)	0.003
Median (Q1, Q3)	0.78 (0.59, 0.89)	0.69 (0.42, 0.83)	
WPAI ^g			
% work time missed due to problem, n			
Patients with missing data, n	80	34	
Patients included, n	16	5	
Mean (SD)	10.0 (10.5)	22.2 (26.0)	0.133
Median (Q1, Q3)	9.2 (0, 18.3)	15.0 (9.1, 20.0)	
% impairment while working due to problem, n			
Patients with missing data, n	80	34	
Patients included, n	16	5	
Mean (SD)	35.0 (20.3)	58.0 (11.0)	0.027
Median (Q1, Q3)	30.0 (25.0, 45.0)	50.0 (50.0, 70.0)	
% overall work impairment due to problem, n			
Patients with missing data, n	80	34	
Patients included, n	16	5	
Mean (SD)	39.9 (22.8)	65.8 (16.4)	0.031
Median (Q1, Q3)	38.1 (28.3, 54.3)	60.0 (54.6, 74.5)	

(Continued)

Table 3 (Continued).

	Triple Therapy n=96	Symptomatic SET n=39	p Value ^a
% activity impairment due to problem, n			
Patients with missing data, n	1	0	
Patients included, n	95	39	
Mean (SD)	52.1 (21.9)	64.9 (21.4)	0.003
Median (Q1, Q3)	50.0 (40.0, 70.0)	70.0 (50.0, 80.0)	

Notes: ^aStatistical analyses were conducted using Student's t-tests, Fisher's Exact tests and Pearson's Chi-Squared tests as appropriate ($p < 0.05$ indicated in bold). ^bComprises 8 items: Cough, Phlegm, Chest tightness, Breathlessness, Activities, Confidence, Sleep, and Energy, with a 0–5 scale response per item. A score of 0 represents no impairment and a score of 40 represents severe impairment. ^cThe cough item on the CAT is scored on a scale of 0 ("I never cough") to 5 ("I cough all the time"). ^dThe phlegm/sputum item on the CAT is scored on a scale of 0 ("I have no phlegm in my chest at all") to 5 ("My chest is completely full of phlegm"). ^eThe EQ-5D-VAS is scored on a scale of 0 (the worst imaginable health state) to 100 (the best imaginable health state). ^fThe EQ-5D-5L is scored on a scale of 0 (the worst imaginable health state, with the allowance of negative values to be assigned to health states that are considered worse than dead) to 1 (the best imaginable health state). ^gThe WPAL is scored on a scale of 0 (no impairment) to 100 (severe impairment).

Abbreviations: CAT, COPD Assessment Test; EQ-5D-5L, European Quality of Life-5 Dimension-5 Level; EQ-5D-VAS, European Quality of Life-Visual Analogue Scale; HRQoL, health-related quality of life; Q, quartile; SD, standard deviation; SET, smoking, exacerbating and on triple therapy; WPAL, work productivity and activity impairment.

Table 4 Physician Involvement and Health Care Resource Utilization

	Triple Therapy n=96	Symptomatic SET n=39	p Value ^a
Physician involvement			
Frequency of HCP visits during the last 12 months			
Mean (SD)	6.5 (3.6)	7.1 (3.8)	0.400
Median (Q1, Q3)	6.0 (3.0, 9.0)	6.0 (5.0, 9.0)	
Initial HCP, n (%) ^b			
Patients with missing data, n	2	1	
Patients included, n	94	38	
PCP	22 (23.4)	14 (36.8)	0.198
Respiratory specialist	69 (73.4)	22 (57.9)	
Emergency department physician	2 (2.1)	2 (5.3)	
Diagnosing HCP, n (%) ^c			
Patients with missing data, n	2	0	
Patients included, n	94	39	
PCP	4 (4.3)	6 (15.4)	0.063
Respiratory specialist	89 (94.7)	33 (84.6)	
HCP that initiated maintenance treatment, n (%)			
Patients with missing data, n	1	0	
Patients included, n	95	39	
PCP	4 (4.2)	3 (7.7)	0.415
Respiratory specialist	91 (95.8)	36 (92.3)	
HCP currently responsible for treatment decisions, n (%)			
PCP	4 (4.2)	1 (2.6)	1.000
Respiratory specialist	96 (100.0)	39 (100.0)	
Hospital service utilization			
Hospital level, n (%)			
CHC	5 (5.2)	2 (5.1)	0.515
Secondary	28 (29.2)	9 (23.1)	
Tertiary	63 (65.6)	28 (71.8)	

(Continued)

Table 4 (Continued).

	Triple Therapy n=96	Symptomatic SET n=39	p Value^a
Patients required hospital stays due to exacerbation during the last 12 months, n (%)	45 (46.9)	32 (82.1)	0.495
Mean (SD) number of nights	5.0 (4.7)	8.6 (9.0)	0.027
Median (Q1, Q3) number of nights	5.0 (2.0, 6.0)	5.5 (4.0, 10.0)	
Patients required ICU stays due to exacerbation during the last 12 months, n (%)	16 (16.7)	8 (20.5)	0.453
Mean (SD) number of nights	1.9 (2.3)	2.4 (2.0)	0.600
Median (Q1, Q3) number of nights	1.0 (1.0, 2.0)	2.0 (1.0, 2.5)	

Notes: ^aStatistical analyses were conducted using Student's *t*-tests, Fisher's Exact tests and Mann–Whitney *U*-tests as appropriate (*p* < 0.05 indicated in bold). ^bIn the triple therapy cohort, initial HCPs also included respiratory nurse (n=1, 1.1%). ^cIn the triple therapy cohort, diagnosing HCPs also included emergency department physician (n=1, 1.1%).

Abbreviations: CHC, community health center; HCP, health care professionals; PCP, primary care physician; Q, quartile; SD, standard deviation; SET, smoking, exacerbating and on triple therapy.

required hospital and ICU stays, respectively, due to COPD exacerbations during the last 12 months; mean (SD) numbers of nights spent in hospital and ICU due to exacerbations were 8.6 (9.0) and 2.4 (2.0), respectively (Table 4).

Discussion

This cross-sectional real-world study identified and characterized a subpopulation of patients in China who had a history of smoking and experienced COPD symptoms and exacerbations while receiving triple inhaled therapy. Results of this study revealed that even with the highest-level inhaled treatment of triple therapy, these patients were still suffering from substantial disease burden from COPD, as reflected by the heavy symptom burden and high exacerbation frequencies. Considerable unmet needs concerning suboptimal disease control were revealed, as both physicians and patients reported low levels of satisfaction with COPD control. Poor HRQoL and detrimental impact on daily lives and work productivity were observed. These patients also experienced high numbers of HCRU events, indicating a high economic burden.

This study identified that among all patients with COPD receiving triple therapy, 28.9% (39/135) had a history of smoking and experienced COPD symptoms and exacerbations. This percentage is numerically comparable to the 33.1% (399/1205) in the global cohort of this DSP.¹⁷ However, it has to be pointed out that only 16.0% (135/844) of patients in the current study were receiving triple therapy, numerically lower than the 27.6% in the global DSP cohort and the 43.0% reported in a similar study conducted in the UK.^{11,17} The relative low usage of triple therapy among all patients with COPD in China was further supported by a recent multicentre, observational study (17.7%, 417/2358).⁸ Such low usage of triple therapy might reflect poor implementation of guideline-directed medical therapy (GDMT) and suboptimal disease management within the country.⁸ Considering that triple therapy is primarily used as an escalation treatment instead of initial treatment in real-world clinical settings in China,²⁴ patients who are not adequately treated with dual therapies might not be accurately identified by physicians during their routine clinical visits, which requires a careful assessment of exacerbation histories as well as blood eosinophil levels, and thus not receiving triple therapy. Indeed, only 40.6% (39/96) of patients in the triple therapy cohort had BEC results available; the suboptimal testing rate of BEC may potentially limit the number of patients who are being escalated to triple therapy. Medication accessibility may also be an underlying reason, while triple therapy is increasingly available in tertiary hospitals, its access in community health center or secondary hospitals might still be limited. Economic considerations may also play a role in the low usage of triple therapy, as patients may opt for lower-cost therapies instead of triple therapy to reduce financial burden.

High symptom frequency was observed, with 29.0% of patients in the symptomatic SET cohort and 7.7% of patients in the triple therapy cohort experiencing COPD symptoms during the day every day. Symptomatic SET patients in the current study had 2.3 exacerbations on average in the 12 months prior to survey date, significantly higher than that in the triple therapy cohort (averaged 1.3 exacerbations) in the same time frame. Although RCTs such as IMPACT and ETHOS have reported the efficacy of triple inhaled therapy in reducing exacerbations,^{25,26} physicians still perceived 87.2% of patients in the symptomatic SET cohort as having high future exacerbation risks, significantly higher than that perceived in the triple therapy cohort. This result suggests that triple therapy may be either ineffective or at least inadequate for

preventing future exacerbations in patients in the symptomatic SET cohort. It was noteworthy that, despite the fact that all patients in the symptomatic SET cohort were symptomatic and experienced exacerbations, physicians considered that almost 70% of patients had at least somewhat controlled COPD (completely controlled: 2.6%; well controlled: 28.2%; somewhat controlled: 38.5%); this overestimation of COPD control may hinder the treatment escalation in these patients, resulting in under-treatment that in turn adds to the overall disease burden. Taken together, these results indicate notably heavy disease burden and substantial unmet needs among the patients in the symptomatic SET cohort in China, mirroring the findings from the global cohort of this DSP.¹⁷

Several real-world studies have reported significant improvement in PROMs, including CAT scores and measurements of HRQoL, after the treatment with triple therapy among patients with COPD.^{27–30} However, few studies have examined these PROMs specifically among patients who experienced symptoms and frequent exacerbations while receiving triple therapy,^{12,17} especially in China. In the current study, all patients in the symptomatic SET cohort had CAT scores ≥ 10 with a mean (SD) score of 25.7 (7.1), and these patients exhibited poor HRQoL including impairment in work and activity, with numerous aspects of daily lives such as sleep, mood and exercise all affected. These results are consistent with prior research, which has revealed elevated CAT scores in patients with frequent exacerbations³¹ and has highlighted the significant, deleterious effects that COPD exacerbations have on HRQoL, particularly with regard to activity impairment and mental health.³² As such, results from the current study comprehensively demonstrate the impairment of COPD on health status from the patients' perspective, highlighting the unmet need for improvement in the wellbeing of those experiencing symptoms and exacerbations while receiving triple therapy in China.

Heavy disease burdens of COPD represent a large component of socioeconomic burden.⁹ In the current study, the incidence of HCRU events was notably high for patients in the symptomatic SET cohort: 82.1% and 20.5% of patients required hospital and ICU stays due to exacerbations, respectively. In line with these findings, an observational study in the UK reported a substantially higher number of HCRU events in patients who experienced exacerbations despite receiving maximal triple inhaled therapy compared to the overall patients with COPD.¹¹ Considering the large number of patients with COPD in China, the overall costs associated with HCRU among these symptomatic SET patients is expected to be significantly high.

Findings from our study reinforce the notion that triple inhaled therapy may not provide adequate treatment for patients who experience symptoms and exacerbations while on triple therapy, highlighting the urgent need for novel therapeutic options.^{11,33} Previous studies have proposed that eosinophil-targeting biologics may be a promising treatment option, as eosinophilic inflammation might be associated with inadequate responses to triple therapy.^{11,33} However, it should be pointed out that in the current study, only 27.8% of patients in the symptomatic SET cohort had BEC ≥ 300 cells/ μ L, statistically comparable with the 23.1% reported in the triple therapy cohort. The relatively small number of patients with BEC results available may have limited the interpretation of this result in our study. Interestingly, a previous global study also reported similar results: among patients receiving triple therapy and had historical moderate/severe exacerbations during past one year, 33.5% of them had BEC ≥ 300 cells/ μ L.³³ While patients with high BEC may be good candidates for eosinophil-targeting biologics, it remains unknown whether such biologics represent the best treatment option for those without elevated BEC. Epithelial-derived alarmins, on the other hand, are upstream regulators of both type 2 (T2)-high and T2-low immune responses in airway inflammation.¹⁴ Biologics targeting alarmins (including TSLP and IL-33) might serve as an alternative treatment option,¹⁴ facilitating a more tailored therapeutic strategy based on eosinophilic phenotypes.¹³

While awaiting the advent of more efficacious treatment options, there are other aspects in the comprehensive management of COPD that can be enhanced. For example, non-pharmacological treatment as outlined in the GOLD recommendations is a key part of COPD management and needs to be strengthened.⁷ In the current study, 28.2% of the symptomatic SET patients were current smokers, highlighting a need for patient education and assistance in smoking cessation. Viral infection was one of the most common exacerbation triggers, reported in 52.6% of the symptomatic SET patients in this study; vaccination against common respiratory viruses should therefore be offered as part of COPD management. Moreover, multidisciplinary management and multiple treatment modalities on both symptoms and emotions together with holistic assessment are also recommended.³⁴ Also noteworthy is the deviation from GDMT observed in the current study, as around one-fourth of patients received traditional Chinese medicine. In fact,

discrepancies between the real-world treatment patterns and the GDMT were also reported in a recent nationwide, multicentre study in China, highlighting a need for improvement in standardization of disease management.⁸

This study had several limitations. Firstly, participation of Adelphi COPD DSP surveys was influenced by physicians' willingness to complete the surveys and minimum physician exclusion criteria were employed, resulting in potential physician selection bias. Patient selection bias was also possible, as patient enrolment relied on physicians' subjective judgement and clinical perception rather than standardized diagnostic codes. To mitigate the patient selection bias, each physician was required to enrol their next five consecutively consulting eligible patients; however, this non-random sampling method limits the broader generalizability of the findings. Secondly, the retrospective nature of this study may have introduced recall bias from the patient. In order to minimize the recall bias, data were collected at the time of each patient's consultation and physicians were able to refer to patients' medical records while completing the patient record forms. Thirdly, missing data were not imputed, resulting in varying patient numbers in some analyses. For example, the numbers of patients with available spirometry or BEC results were small, and results of these outcomes should be considered exploratory and warrant further investigation in larger clinical studies. Fourthly, the symptoms required for inclusion in the symptomatic SET cohort, namely frequent productive cough and sputum (in the four weeks preceding survey date), were physician-reported and based on medical records instead of objective measures such as modified Medical Research Council (mMRC) Dyspnea Scale. Similarly, several outcomes in the current study (the assessment of COPD control, COPD symptoms and impact of COPD on patients' daily activity during the last four weeks) were determined by physician's clinical understanding of the patient's condition. Consequently, these results may be influenced by physician's subjectivity. Nevertheless, these subjective judgements by physicians served as the primary driver for treatment adjustment and reflected the real-world clinical decision-making. Lastly, comorbid bronchiectasis was not assessed. Despite the above-mentioned limitations, real-world studies are pivotal in highlighting areas of concern that are not addressed in clinical trials. Patients included in clinical trials represent a small proportion of the consulting population due to age restrictions and failure to meet stringent eligibility criteria. In contrast, patients treated in the real-world setting encompassing a more heterogeneous spectrum of patients and as a result, data from real-world studies serve as a vital complement to clinical trials and provide insight into the effectiveness of interventions in a broad patient population in routine clinical practice.

Conclusions

This study demonstrated the presence of a subpopulation of patients in China who experienced COPD symptoms and frequent exacerbations while receiving the highest level of inhaled treatment with triple therapy. These patients had heavy disease and socioeconomic burden and large unmet needs, highlighting a need for more effective treatment options. These patients may benefit from novel biologics based on tailored therapeutic strategies, together with an improvement in guideline-directed disease management approaches.

Data Sharing Statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at <https://www.astrazenecaclinicaltrials.com/our-transparency-commitments/>.

Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at <https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/>. AstraZeneca Vivli member page is also available outlining further details: <https://vivli.org/ourmember/astrazeneca/>.

Ethics Approval and Informed Consent

This study was submitted to the Pearl Institutional Review Board (protocol number: #22-ADRW-147). Ethics approval was waived as this was a healthcare market research survey. Written informed consent was obtained from all participating patients during the survey.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

TP and FB are employees of Adelphi Real World.

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