Exacerbation Frequency, COPD Symptoms, and Health-Related Quality of Life of COPD Patients According to Post-Bronchodilator FEV_1 – A Post-hoc Analysis of Pooled Data from Two Cross-Sectional Studies

Chee-Shee Chai (cschai@unimas.my)
University Malaysia Sarawak
Diana-Leh-Ching Ng
University Malaysia Sarawak
Sumastika Bt Mos
University Malaysia Sarawak
Muhammad Amin B Ibrahim
University Technology MARA
Seng-Beng Tan
University of Malaya
Yong-Kek Pang
University of Malaya
Chong-Kin Liam
University of Malaya

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Abstract

Background:

This study aimed to compare and correlate the post-bronchodilator forced expiratory volume in one second (PB-FEV_1), exacerbation frequency, and scores of modified Medical Research Council (mMRC), COPD Assessment Tool (CAT), and St George's Respiratory Questionnaire for COPD (SGRQ-c) of COPD patients.

Methods:

This was a post-hoc analysis of pooled data from two cross-sectional studies conducted from 1st June 2017 to 31st May 2018 at the respiratory clinic of University of Malaya Medical Center, and from 23rd January 2018 to 22nd January 2019 at the outpatient clinics of the Serian Divisional Hospital and Bau District Hospital in Malaysia, respectively. The parameters measured included PB-FEV_1, exacerbation frequency, mMRC, CAT, and SGRQ-c. Descriptive, association and correlation statistics were used.

Results:

Of a total of 374 patients, the PB-FEV_1 predicted was < 30% in 85 (22.7%), 30 – 49% in 142 (38.0%), 50 – 79% in 111 (29.7%), and ≥ 80% in 36 (9.6%) patients. Patients with PB-FEV_1 < 30% predicted had significantly more COPD exacerbations than those with PB-FEV_1 30 – 49% predicted ($p < 0.001$), 50 – 79% predicted ($p < 0.001$), and ≥ 80% predicted ($p = 0.002$). The scores of mMRC, CAT and SGRQ-c were not significantly higher in patients with more severe airflow limitation based on PB-FEV_1 ($p = 0.121$ – 0.271).

The PB-FEV_1 predicted had significant small negative correlations with exacerbation frequency ($r = -0.182$, $p < 0.001$), mMRC ($r = -0.121$, $p = 0.020$), and SGRQ-c scores ($r = -0.114$, $p = 0.028$). There was a moderate positive correlation between COPD exacerbation frequency and scores of mMRC, CAT, and SGRQ-c ($r = 0.407$ – 0.482, all $p < 0.001$). There were significant strong positive correlations between mMRC score with CAT ($r = 0.727$) and SGRQ-c scores ($r = 0.847$), and CAT score with SGRQ-c score ($r = 0.851$) (all $p < 0.001$).

Conclusions:

In COPD patients, different severity of airflow limitation was not associated with significant differences in the dyspnea symptom and HRQOL. Exacerbation was significantly more frequent in patients with very severe airflow limitation only. The correlation between airflow limitation with exacerbation, dyspnea symptom, and HRQOL was weak.

Background

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable airway disease characterized by persistent respiratory symptoms and airflow limitation caused by prolonged exposure to noxious particles or gases.(1) The estimated global prevalence of COPD is 13.1% with a continent-based prevalence of 12.4% in Europe, 13.2% in the Americas, 13.5% in Asia, 11.6% in Oceania, and 13.9% in Africa.(2) Worldwide, COPD is currently the fourth leading cause of mortality resulting in 3.2 million deaths annually and the second leading cause of disease burden accounting for 63.9 million disability-adjusted life-years.(3)

Forced expiratory volume in one second (FEV_1), exacerbation, dyspnea symptom, and health-related quality of life (HRQOL) are the common parameters used in the classification of COPD. FEV_1 measurement is essential in estimating the severity of airflow limitation in asthma and COPD. It is widely used by physicians for the diagnosis, staging, treatment monitoring, and determining the prognosis of COPD patients.(4) FEV_1 measurement is simple, quick, objective, reproducible, consistent, and with a well-established reference range.(5) Exacerbation frequency is a strong predictor of decline in lung function, reduced exercise tolerance, poor quality of life, and higher mortality.(6, 7) Dyspnea, the commonest symptom experienced by COPD patients, is associated with decreased physical activity, reduced HRQOL, and increased mortality.(8) HRQOL is defined as an individual's happiness or satisfaction towards his or her life which is affected by physical, mental, emotional, and social health.(9) A poor HRQOL is associated with dyspnea symptom, physical impairment, mental health problems, hospital admission, and mortality.(10, 11) For COPD, modified Medical Research Council (mMRC) is the recommended assessment tool for dyspnea symptom while HRQOL can be measured by using St George's Respiratory Questionnaire for COPD (SGRQ-c) or the abbreviated COPD Assessment Test (CAT).

In real-world practice, the parameters and assessment tools used to classify COPD are not without limitations. To date, there is no recommendation to perform spirometry regularly during the routine follow-up of COPD patients. Recall of exacerbation frequency is subjected to the patients' memory. Thresholds for patients presenting to the healthcare facility during a worsening of respiratory symptoms are different. Moreover, the threshold for healthcare workers to initiate steroid/antibiotic or admit patients to the hospital can also differ. Hospital admission may be dependent on bed availability. mMRC, CAT, and SGRQ-c are very subjective methods of assessment, as different people may comprehend their symptoms, activities, and disease impacts differently. These parameters are also dynamic and mMRC, CAT, or SGRQ-c scores can vary over time.

Therefore, we decided to conduct this analysis to look into the FEV_1, exacerbation frequency, dyspnea symptom, and HRQOL of Malaysian COPD patients. The primary objective of this analysis was to compare the exacerbation frequency, and the scores of mMRC, CAT, and SGRQ-c of COPD patients according to the post-bronchodilator forced expiratory volume in one second (PB-FEV_1). The score of each component of SGRQ-c based on PB-FEV_1 was also analyzed. The correlation between PB-FEV_1, exacerbation frequency, and the scores of mMRC, CAT, and SGRQ-c was the secondary objective.

Methods

Study Design and Patients:

This is a post-hoc analysis of pooled data from two cross-sectional studies that we previously conducted in Malaysia, the results of which had been published separately.(12, 13) The first study involving 189 patients was conducted from 1st June 2017 to 31st May 2018 at the respiratory clinic of the University of Malaya Medical Center (UMMC), a tertiary teaching hospital located in Kuala Lumpur.(12) The second study involving 185 patients was conducted from 23rd January 2018 to 22nd January 2019 at the outpatient clinics of the Serian Divisional Hospital and Bau District Hospital, both of which were primary healthcare centers in the southern part of the state of Sarawak.(13) Both studies aimed to compare the HRQOL of patients with stable COPD according to their clinical phenotypes.

The inclusion criterion of the first study was patients aged 40 years and above with the ratio of PB-FEV_1 to post-bronchodilator forced vital capacity (PB-FVC) of < 0.7; while the inclusion criterion for the second study was patients aged 35 years and above with the ratio of PB-FEV_1 to PB-FVC in six seconds (PB-FVC_6) of < 0.7. Otherwise, both studies had similar exclusion criteria which included patients with clinical or radiological diagnoses of other chronic lung diseases (such as bronchiectasis and interstitial lung disease), active tuberculosis, and lung tumors. The sample size was calculated based on the formula for ANCOVA, in which alpha was 0.05, power was 0.9, the number of the group was 4, and the mean value referred to the exacerbation frequency. A minimum of 52 subjects were required in each group, therefore the estimated minimum sample size was 208 patients. Written informed consent for the studies and publication was obtained from all participating patients. The studies were conducted in accordance with the Declaration of Helsinki. Ethics approval was obtained from the Medical Research and Ethics Committee of the UMMC (MECID. No 2017814-5496) for the first study and from the National Medical Research Registry of Malaysia (NMRR-17-2549-38621) for the second study.

Procedure:

In both studies, eligible patients were consecutively identified from the respective clinics. Spirometry was performed according to the American Thoracic Society and European Respiratory Society guidelines. Patient demographic data and clinical characteristics were obtained by face-to-face interviews and from the case notes. Demographic data included age, gender, ethnicity, smoking status, smoking quantity, and history of biomass smoke exposure. Clinical characteristics included the number of COPD exacerbations over the past one year and dyspnea symptom according to mMRC.

PB-FEV_1 was expressed in percent of predicted value based on the patients' age, gender, ethnicity, and height. Patients were divided into four groups according to the severity of airflow limitation based on PB-FEV_1: < 30% predicted (very severe); 30–49% predicted (severe); 50–79% predicted (moderate); and ≥ 80% predicted (mild).(1) The ethnic composition of Malaysians includes Malay, Chinese, Indian, and others (such as natives). A never smoker was defined as an individual who smoked < 100 cigarettes in a

lifetime; while former or current smokers were individuals who had smoked ≥ 100 cigarettes in a lifetime.(14) An former smoker was one who had quit smoking for more than a year at the time of interview. Smoking quantity was calculated in pack-year (number of cigarettes smoked per day/20 x number of years smoking). Exposure to biomass smoke was defined as ever exposure to smoke from the burning of wood, crop, or charcoal for ≥ 100 hours per year.(15)

An exacerbation of COPD was defined as acute worsening of the patient's condition beyond normal day-to-day variation and may warrant additional treatment.(16) Only moderate and/or severe exacerbations over the past one year before the interview that predicted the risk of future exacerbations were taken into account. A moderate exacerbation was one that required outpatient treatment with corticosteroids and/or antibiotics while a severe exacerbation was one that warranted hospitalization.(17) mMRC score was 0 if dyspnea was present only on strenuous activity, 1 when dyspnea was experienced when walking uphill, 2 when dyspnea led to walking slower than people of the same age, 3 when dyspnea led to stop for breath after walking ≤ 100 meters on level ground, and 4 when dyspnoeic during dressing or undressing or being housebound because of dyspnea.(1) Low symptom level referred to a mMRC score of 0–1 while high symptom level referred to a mMRC score of 2–4.

Patients were instructed to answer the CAT and SGRQ-c questionnaires independently to assess their HRQOL. These questionnaires were available in the original English version or validated Malay and Chinese versions. The CAT questionnaire consisted of eight items: CAT 1 – cough; CAT 2 – sputum; CAT 3 – chest tightness; CAT 4 – dyspnea; CAT 5 – activity limitation; CAT 6 – confidence to leave home; CAT 7 – sleep; and CAT 8 – energy.(18) The score of each item ranged from 0 to 5. The total score of CAT ranged from 0 to 40, with normal individuals having a total score of ≤ 6. The SGRQ-c questionnaire assessed of three components: symptoms (questions 1–7); activity (questions 9 and 12); and impacts (questions 8, 10, 11, 13, and 14).(19) The total score and score of each component of SGRQ-c ranged from 0 to 100%. The SGRQ-c score for normal individuals was ≤ 6% for total; ≤ 12% for symptoms; ≤ 9% for activity; and ≤ 2% for impacts.(20) For both questionnaires, higher scores indicated a poorer HRQOL.

Statistical analysis

Categorical variables were expressed as percentages while continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range. The difference between groups for the categorical variables was compared using the chi-squared test, with post-hoc analysis taking adjusted standardized residual of > 2 as significant. The difference between more than two groups for the continuous variables was compared using the one-way ANOVA test or Kruskal-Wallis H test. The post-hoc analysis for the former was the Tukey test and for the latter was Dunn's procedure with Bonferroni adjustment. The correlation of continuous variables was calculated using Pearson or Spearman correlation test followed by linear regression test. The correlation coefficient (r) was defined as small or weak (0.10–0.29); medium (0.30–0.49); and large or strong (≥ 0.50). A 2-sided p-value of less than 0.05 was considered significant. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS for Windows version 25.0, SPSS Inc, Chicago, IL, USA).

Results

Demographic and clinical characteristics

A total of 374 patients were included in the analysis (Fig. 1). Their demographic and clinical characteristics are shown in Table 1. The overall mean PB-FEV_1 was 47.5 ± 21.3% predicted. The PB-FEV_1 was < 30% predicted in 85 patients (22.7%), 30–49% predicted in 142 patients (38.0%), 50–79% predicted in 111 patients (29.7%), and ≥ 80% predicted in 36 patients (9.6%). The proportion of patients with a history of biomass smoke exposure was significantly higher in those with PB-FEV_1 < 30% predicted (48.2%) compared to those with less severe airflow limitation [(PB-FEV_1 30–49% (31.7%), PB-FEV_1 50–79% (35.1%), and PB-FEV_1 ≥ 80% (19.4%), p = 0.012]. Otherwise, the age, gender, ethnicity, smoking status, and smoking quantity of the patients were not significantly different across the different categories of severity of airflow limitation based on PB-FEV_1.

Table 1
Demographic and clinical characteristics of COPD patients according to the severity of airflow limitation based on PB-FEV_1

Characteristic	All COPD patients, N = 374	Severity of airflow limitation based on PB-FEV_1 (% predicted)				p-value
		< 30%	30–49%	50–79%	≥ 80%	
		Number of COPD patients (% of total COPD patients)				
		85 (22.7)	142 (38.0)	111 (29.7)	36 (9.6)	
Age (mean ± SD, 95% CI), years	67.3 ± 11.8; 66.1–68.5	65.7 ± 10.5; 63.4–67.9	67.7 ± 11.4; 65.8–69.6	67.2 ± 12.4; 64.9–69.5	70.0 ± 13.7; 65.1–74.4	0.345
Gender (n, %)	317 (84.8)	77 (90.6)	120 (84.5)	90 (81.1)	30 (83.3)	0.326
Male	57 (15.2)	8 (9.4)	22 (15.5)	21 (18.9)	6 (16.7)	
Female						
Ethnicity (n, %)	104 (27.8)	24 (28.2)	42 (29.6)	27 (24.3)	11 (30.6)	0.283
Malay	104 (27.8)	18 (21.2)	37 (26.1)	33 (29.7)	16 (44.4)	
Chinese	31 (8.3)	6 (7.1)	14 (9.9)	11 (9.9)	0	
Indian	135 (36.1)	37 (43.5)	49 (34.5)	40 (36.0)	9 (25.0)	
Others						
Smoking status (n, %)	69 (18.4)	13 (15.3)	27 (19.0)	22 (19.8)	7 (19.4)	0.422
Never smoker	201 (53.7)	45 (52.9)	78 (54.9)	54 (48.6)	24 (66.7)	
Former smoker	104 (27.8)	27 (31.8)	37 (26.1)	35 (31.5)	5 (13.9)	
Current smoker						
Smoking quantity (mean ± SD, 95% CI), pack-years	30.2 ± 27.6; 27.4–33.0	27.1 ± 22.3; 22.3–31.9	30.5 ± 29.5; 25.6–35.3	32.6 ± 29.3; 27.1–38.1	28.4 ± 25.6; 19.8–37.1	0.559

Abbreviations: COPD, chronic obstructive pulmonary disease; PB-FEV_1, post-bronchodilator forced expiratory volume in one second;

mMRC, modified Medical Research Council; SD, standard deviation; CI, confidence interval.

Characteristic	All COPD patients, N = 374	Severity of airflow limitation based on PB-FEV_1 (% predicted)				p-value
		< 30%	30–49%	50–79%	≥ 80%	
		Number of COPD patients (% of total COPD patients)				
		85 (22.7)	142 (38.0)	111 (29.7)	36 (9.6)	
Biomass smoke exposure (n, %)	242 (64.7)	44 (51.8)	97 (68.3)	72 (64.9)	29 (80.6)	0.012
No	132 (35.3)	41 (48.2)	45 (31.7)	39 (35.1)	7 (19.4)	
Yes						
Frequency of COPD exacerbation in the past one year (mean ± SD, 95% CI)	2.2 ± 4.2;	4.0 ± 7.0;	1.8 ± 2.9;	1.6 ± 2.7;	1.1 ± 1.8;	< 0.001
	1.7–2.6	2.5–5.5	1.3–2.2	1.1–2.1	0.5–1.8	
All exacerbations	1.4 ± 3.1;	3.0 ± 5.5;	1.0 ± 1.8;	1.0 ± 1.8;	0.7 ± 1.1;	< 0.001
Moderate	1.1–1.7	1.8–4.2	0.7–1.3	0.6–1.3	0.3–1.1	0.106
Severe	0.8 ± 1.5;	1.1 ± 2.0;	0.8 ± 1.4;	0.6 ± 1.3;	0.5 ± 0.8;	
	0.6–0.9	0.6–1.5	0.6–1.0	0.4–0.9	0.2–0.8	
mMRC score (n, %)	181 (48.4)	37 (43.5)	65 (45.8)	57 (51.4)	22 (61.1)	0.271
0–1						
2–4	193 (51.6)	48 (56.5)	77 (54.2)	54 (48.6)	14 (38.9)	

Abbreviations: COPD, chronic obstructive pulmonary disease; PB-FEV_1, post-bronchodilator forced expiratory volume in one second;

mMRC, modified Medical Research Council; SD, standard deviation; CI, confidence interval.

PB-FEV_1, COPD exacerbation, and dyspnea symptom

The frequency of all and moderate COPD exacerbations was significantly different across the patient groups with different severity of airflow limitation based on PB-FEV_1 (both p values < 0.001). Patients with PB-FEV_1 < 30% predicted had significantly more frequent exacerbation of all types than those with PB-FEV_1 30–49% predicted (4.0 ± 7.0 versus 1.8 ± 2.9, p < 0.001), PB-FEV_1 50–79% predicted (4.0 ± 7.0 versus 1.6 ± 2.7, p < 0.001), and PB-FEV_1 ≥ 80% predicted (4.0 ± 7.0 versus 1.1 ± 1.8, p = 0.002). Moderate exacerbations were also significantly more frequent in patients with PB-FEV_1 < 30% predicted than that of patients with PB-FEV_1 30–49% predicted (3.0 ± 5.5 versus 1.0 ± 1.8, p < 0.001), PB-FEV_1 50–79% predicted (3.0 ± 5.5 versus 1.0 ± 1.8, p < 0.001) and PB-FEV_1 ≥ 80% predicted (3.0 ± 5.5 versus 0.7 ± 1.1, p = 0.001). When compared between the COPD patients with PB-FEV_1 30–49% predicted, PB-FEV_1 50–79% predicted,

and PB-FEV_1 ≥ 80% predicted, there was no significant difference in the frequency of all (p = 0.851–0.984) and moderate exacerbation (p = 0.970–0.999).

Even though patients with more severe airflow limitation had more frequent severe exacerbations, the difference was not significant (p = 0.106). Similarly, a higher percentage of patients with more severe airflow limitation were more symptomatic from dyspnea (mMRC 2–4) but the difference across the patient groups was also not significant (p = 0.271).

PB-FEV_1 and HRQOL

The patients' CAT and SGRQ-c scores were higher than normal regardless of their PB-FEV_1 (Table 2). Patients with more severe airflow limitation based on their PB-FEV_1 had higher total scores of CAT and SGRQ-c compared to those with less severe airflow limitation but the difference was not statistically significant (p = 0.230, and p = 0.121, respectively).

Table 2
CAT and SGRQ-c score of COPD patients according to the severity of airflow limitation based on PB-FEV_1

HRQOL parameters	All patients	Severity of airflow limitation based on PB-FEV_1 (% predicted)				p-value
		< 30%	30–49%	50–79%	≥ 80%	
CAT score, (means ± SD, 95% CI)	14.8 ± 10.1; 13.8–15.8	15.7 ± 11.1; 13.3–18.1	14.9 ± 10.1; 13.2–16.5	15.1 ± 9.9; 13.2–17.0	11.6 ± 8.1; 8.9–14.4	0.230
SGRQ-c score, % (means ± SD, 95% CI)						
Total	40.4 ± 26.0; 37.8–43.1	43.6 ± 29.2; 37.3–49.9	41.3 ± 27.1; 36.8–45.8	39.8 ± 23.7; 35.4–44.3	31.4 ± 18.5; 25.1–37.7	0.121
Symptoms	42.7 ± 26.4; 40.0–45.3	47.0 ± 29.2; 40.7–53.3	44.1 ± 27.8; 39.5–48.8	41.1 ± 22.7; 36.8–45.4	31.8 ± 21.4; 24.6–39.1	0.026
Activities	48.6 ± 30.4; 45.5–51.7	53.8 ± 32.5; 46.8–60.8	50.4 ± 32.1; 45.0–55.7	44.5 ± 27.2; 39.4–49.7	42.2 ± 26.1; 33.3–51.0	0.087
Impact	34.8 ± 29.4; 31.8–37.8	36.5 ± 32.9; 29.4–43.6	34.9 ± 29.2; 30.1–39.8	36.6 ± 28.8; 31.2–42.0	25.0 ± 21.5; 17.7–32.2	0.192

Abbreviations: HRQOL, health-related quality of life; CAT, COPD Assessment Tool; SGRQ-c, St George's Respiratory Questionnaire for COPD; COPD, chronic obstructive pulmonary disease; PB-FEV_1, post-bronchodilator forced expiratory volume in one second; SD, standard deviation; CI, confidence interval.

There was no significant difference in the scores of each of the SGRQ-c components (except symptoms, p = 0.026) according to the severity of airflow limitation based on PB-FEV_1. For the symptoms

component, patients with PB-FEV_1 < 30% predicted had a significantly higher score than those with PB-FEV_1 ≥ 80% predicted (47.0 ± 29.2 versus 31.8 ± 21.4, p = 0.020).

Correlation and regression of PB-FEV_1, COPD exacerbation frequency, dyspnea symptom, and HRQOL

There were weak negative correlations between PB-FEV_1 and exacerbation frequency (r = − 0.182, p < 0.001), mMRC score (r = − 0.121, p = 0.020), and SGRQ-c score (r = − 0.114, p = 0.028), respectively (Table 3). There was no correlation between PB-FEV_1 and CAT score (r = − 0.072, p = 0.162). Exacerbation frequency was positively correlated to the mMRC, CAT, and SGRQ-c scores, respectively with moderate co-efficient (r = 0.407–0.482, all p < 0.001). There were strong positive correlations between mMRC score and CAT score (r = 0.727) and SGRQ-c score (r = 0.847), respectively while CAT score was strongly correlated to SGRQ-c score (r = 0.851) (all p < 0.001).

Table 3
Pearson correlation of PB-FEV_1 with COPD exacerbation frequency and scores of mMRC, CAT, and SGRQ-c, respectively

Variables	N	r	p-value
PB-FEV_1% with exacerbation	374	− 0.183	< 0.001
PB-FEV_1% with mMRC	374	− 0.121	0.020
PB-FEV_1% with CAT	374	− 0.072	0.162
PB-FEV_1% with SGRQ-c	374	− 0.114	0.028
Exacerbation with mMRC	374	0.407	< 0.001
Exacerbation with CAT	374	0.445	< 0.001
Exacerbation with SGRQ-c	374	0.482	< 0.001
mMRC with CAT	374	0.727	< 0.001
mMRC with SGRQ-c	374	0.847	< 0.001
CAT with SGRQ-c	374	0.851	< 0.001

Abbreviations: PB-FEV_1, post-bronchodilator forced expiratory volume in one second; mMRC, modified Medical Research Council; CAT, COPD Assessment Tool; SGRQ-c, St George's Respiratory Questionnaire for COPD; COPD, chronic obstructive pulmonary disease; r, co-efficient.

For linear regression, exacerbation frequency equals to 3.870–0.036(PB-FEV_1%) (R^2 = 0.033) (beta = − 0.183); mMRC equals to 2.085–0.007(PB-FEV_1%) (R^2 = 0.015) (beta = − 0.121); CAT equals to 16.439–0.035(PB-FEV_1%) (R^2 = 0.015) (beta = − 0.072); and SGRQ-c equals to 47.049–0.139(PB-FEV_1%) (R^2 =

0.013) (beta = − 0.114). Other linear regressions involving exacerbation frequency, mMRC, CAT, and SGRQ-c are as shown in Table 4.

Table 4
Linear regression between COPD exacerbation frequency and scores of mMRC, CAT, and SGRQ-c, respectively

Variables	*R*	R^2	Constant	B	SE	beta	t	p-value
PB-FEV_1% and exacerbation	0.183	0.033	3.870	− 0.036	0.010	− 0.183	-3.588	< 0.001
PB-FEV_1% and mMRC	0.121	0.015	2.085	− 0.007	0.003	− 0.121	-2.344	0.020
PB-FEV_1% and CAT	0.072	0.005	16.439	− 0.035	0.025	− 0.072	-1.401	0.162
PB-FEV_1% and SGRQ-c	0.114	0.013	47.049	− 0.139	0.063	− 0.114	-2.204	0.028
Exacerbation and mMRC	0.407	0.165	1.478	0.123	0.014	0.407	8.587	< 0.001
Exacerbation and CAT	0.445	0.198	12.480	1.075	0.112	0.445	9.573	< 0.001
Exacerbation and SGRQ-c	0.482	0.233	33.968	2.999	0.282	0.482	10.619	< 0.001
mMRC and CAT	0.727	0.529	4.656	5.819	0.285	0.727	20.436	< 0.001
mMRC and SGRQ-c	0.847	0.717	10.062	17.425	0.568	0.847	30.676	< 0.001
CAT – SGRQ-c	0.851	0.724	8.039	2.189	0.070	0.851	31.251	< 0.001

Abbreviations: mMRC, modified Medical Research Council; CAT, COPD Assessment Tool; SGRQ-c, St George's Respiratory Questionnaire for COPD; COPD, chronic obstructive pulmonary disease; B, unstandardized beta; SE, standard error.

Discussion

In this analysis, the majority (60.7%) of the COPD patients had severe or very severe airflow limitation. Biomass smoke exposure was significantly more common among patients with very severe airflow limitation. Similarly, all and moderate COPD exacerbations were significantly more frequent in those with very severe airflow limitation. Regardless of airflow limitation severity, the HRQOL of the patients was markedly impaired compared to healthy individuals. Even though patients with more severe airflow limitation had more frequent severe exacerbations, higher dyspnea symptom score, and poorer HRQOL,

these were not significantly different across the severity of airflow limitation groups. Patients with mild airflow limitation had fewer respiratory symptoms than those with very severe airflow limitation. PB-FEV_1 was only weakly associated with exacerbation frequency, dyspnea symptom, and HRQOL; exacerbation frequency was moderately correlated with dyspnea symptom and HRQOL; while dyspnea symptom was strongly correlated with HRQOL.

In the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) study, COPD exacerbations were more frequent and more severe as the severity of airflow limitation increased.(17) The COPD in Five Latin American Cities (PLATINO), and COPD and Systemic Consequences-Comorbidities Network (COSYCONET) reported significantly more frequent exacerbations among patients with severe to very severe airflow limitation.(21, 22) In the Study to Understand Mortality and Morbidity in COPD (SUMMIT), COPD patients in the lowest quantiles (FEV_1 < 53.5% predicted) of airflow limitation reported a significantly higher risk of moderate-to-severe and severe exacerbations.(23) The Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) study and a systemic review by Westwood et al reported an inverse relationship between exacerbation and FEV_1 but the correlation was small ($r = -0.12$, $p < 0.0001$; and $r = -0.27$, $p = 0.049$, respectively).(24, 25) The findings of significantly more frequent exacerbations in our patients with very severe airflow limitation and a small correlation with PB-FEV_1 are consistent with the findings of these studies.

With regard to associations between FEV_1 and dyspnea symptom, Oga et al reported a medium correlation ($r = -0.37$, $p < 0.05$),(26) Huang et al reported a small correlation ($r = -0.234$, $p < 0.001$),(27) while the post-hoc analysis of the Effect of Glycopyrronium or Indacaterol Maleate and Glycopyrronium Bromide Fixed-Dose Combination on Symptoms and Health Status in Patients with Moderate COPD (CRYSTAL) study did not show any correlation ($r = 0.121$).(28) This analysis showed a small correlation between PB-FEV_1 and dyspnea symptom which is only similar to that reported by Huang et al.(27)

Unlike the present study, Izquierdo et al and Hong et al reported that HRQOL was significantly different between patients with different COPD severity.(29, 30) The Clinical COPD Questionnaire (CCQ) was used in the former study while the European Quality of Life Five Dimensions (EQ-5D) was used in the latter. Meanwhile, Agrawal et al and Balcells et al reported a significantly poorer HRQOL assessed by SGRQ-c in patients with stage III /IV and stage IV COPD, respectively.(31, 32) For the association between FEV_1 and HRQOL, Ahmed et al,(33) Burgel et al,(34) and Zamzam et al (35) reported a large correlation (SGRQ-c, $r = -0.86$, $p < 0.001$; SGRQ-c, $r = -0.56$, $p < 0.001$; and $r = -0.65$, $p < 0.001$, respectively); while Deslee et al,(36) Oga et al,(26) and Westwood et al (25) (SGRQ-c, $r = -0.372$, $p < 0.0001$; $r = -0.44$, $p = 0.007$; and $r = -0.46$, $p < 0.001$, respectively), as well as Kim et al (CCQ, $r = -0.35$; and EQ-5D, $r = 0.30$) and Garrido et al (12-Item Short Form Survey: physical component, $r = 0.38$, $p < 0.001$) reported a medium correlation.(37, 38) Sundh et al and Bentsen et al reported a small correlation between FEV_1 and HRQOL (CAT, $r = -0.13$, $p = 0.001$; and EQ-5D, $r = 0.008$, $p < 0.0001$ and 36-Item Short Form Survey: physical, $r = 0.19$, $p = 0.007$; mental, $r = -0.14$, $p = 0.043$, respectively),(39, 40) which were similar to our findings.

Studies have shown patients with frequent COPD exacerbations have significantly worse dyspnea symptom and HRQOL.(6, 41) Our analysis shows a medium correlation between exacerbation frequency and dyspnea symptom as well as HRQOL, consistent with that reported by Kelly et al (mMRC, r = 0.31; and CAT, r = 0.42, both p < 0.0001),(42) Burgel et al (SGRQ-c, r = 0.31, p < 0.001),(34) and Deslee et al (SGRQ-c, r = 0.391, p < 0.0001).(36) To date, a strong correlation between mMRC and HRQOL has been reported by the majority of the studies including that by Deslee et al (SGRQ-c, r = 0.602, p < 0.0001),(36) Ahmed et al (SGRQ-c, r = 0.59, p < 0.001),(33) Burgel et al, (SGRQ-c, r = 0.53, p < 0.01),(34) and Kelly et al (CAT, r = 0.50, p < 0.0001).(42) The present study and another study in Japan by Horita et al (CAT, r = 0.88, p < 0.001) show a very large correlation between mMRC and HRQOL.(43)

FEV_1 is a unidimensional measurement that reflects the pathophysiology of COPD while exacerbation, dyspnea symptom, and HRQOL are multidimensional measurements of COPD consequences from the patients' perspective.(44) This explains the absence or small correlation between FEV_1 with exacerbation, dyspnea symptom, and HRQOL. The interaction between smoking, air pollution, respiratory tract infection, bronchiectasis, blood eosinophil count, the severity of airflow limitation, prior exacerbation, and comorbidities leads to the occurrence of COPD exacerbation.(45) For dyspnea symptom, the mechanisms encompass the interaction of physiological, psychological, and emotional factors of COPD patients.(46) Meanwhile, the HRQOL of COPD patients depends on the interaction of their physical, functional, emotional, social, and economic well-being.(47) The moderate correlation between COPD exacerbation and dyspnea symptom or HRQOL is attributed to the partial overlap between their dimensions. On the other hand, most of the dimensions are overlapped between dyspnea symptom and HRQOL which explains the large correlation. Even though symptoms such as cough, sputum, and wheezing are also assessed, the majority of questions in CAT (CAT 3 – CAT 8) and SQRQ-c (part of symptoms component, most of activity and impact component) still assess dyspnea symptom or their complications as the main outcomes.(18, 19)

The findings from this study suggest that FEV_1 is not a reliable parameter to measure during the follow-up of COPD patients due to its weak correlation with exacerbation, dyspnea symptom, and HRQOL. Exacerbation should be routinely assessed as it is the prognosis hallmark of COPD and is only moderately reflected by the dyspnea symptom or HRQOL. Dyspnea symptom strongly predicts the value of HRQOL. Therefore, during a busy clinic, a simpler and time-saving tool such as mMRC should precede CAT and SGRQ-c. In short, exacerbation and mMRC are the recommended parameters to evaluate during the follow-up of COPD patients. This is in line with the Global Initiative for Chronic Obstructive Lung Disease guidelines that recommend grouping of COPD patients based on exacerbation frequency in the past one year and mMRC or CAT score at diagnosis and evaluating exacerbation and dyspnea symptom during follow-up visits.(1) Only in selected circumstances, spirometry is used to identify alternative diagnoses, suitability for interventional procedures, and to detect a rapid decline in FEV_1.

This study evaluates the core parameters of COPD simultaneously, namely FEV_1, exacerbation, dyspnea symptom, and HRQOL. Even though studies looking at these parameters have been conducted in other

parts of the world, this is one of the very few studies in the South-East Asia region. Data from different regions of the world is needed for various reasons. First, the etiology of COPD can be different. In the present study, biomass smoke exposure was reported in more than one-third of the patients. Even though FEV_1 decline due to biomass smoke exposure is slower,(48) biomass smoke exposure and cigarette smoking have an additive adverse effect on airflow obstruction.(49) Second, genetic heterogeneity can affect the presentation and outcomes of COPD. This study included the population from Peninsular Malaysia and the Island of Borneo. Third, the culture and economic activity of the population could have an impact on the perceived symptom and HRQOL. Other strengths of this study include representative sample was obtained from both the primary and tertiary care centers, as well as a similar methodology was used in both studies, therefore, minimizing any data bias. However, there are several limitations to this study. First, this was a cross-sectional study. HRQOL may vary over time and such variation may not be reflected in a cross-sectional study. Serial changes of FEV_1 may give a better understanding of the exacerbation, dyspnea symptom, and HRQOL. Second, the inclusion criteria of the studies were slightly different in terms of age and definition of fixed airway obstruction. The use of PB-FVC_6 in the second study potentially excludes a proportion of patients with mild COPD. Third, the study outcome was decided later in this post-hoc analysis. However, this study fulfilled the minimum sample size of 208 patients as calculated. Fourth, recall errors in exacerbation frequency cannot be discounted but minimized by counter checks with the medical records and family members. Fifth, the result of this study is only novel for South-East Asia. A future study that prospectively evaluates the FEV_1, exacerbation, dyspnea symptom and HRQOL of COPD patients is expected to mitigate these limitations.

Conclusions

We conclude that different severity of airflow limitation based on PB-FEV_1 was not associated with significant differences in the dyspnea symptom and HRQOL of COPD patients. Exacerbation was significantly more frequent in patients with very severe airflow limitation only. The correlation between the severity of airflow limitation with exacerbation, dyspnea symptom, and HRQOL was weak. Therefore, PB-FEV_1 measurement during the routine clinic follow-up of COPD patients does not provide additional information on top of dyspnea symptom or CAT scores and exacerbation history that may influence treatment decisions.

Abbreviations

COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in one second; mMRC, modified Medical Research Council; CAT, COPD Assessment Tool; HRQOL, health-related quality of life; SGRQ-c, St George's Respiratory Questionnaire for COPD; PB-FEV1, post-bronchodilator FEV_1; UMMC, University Malaya Medical Center; PB-FVC, post-bronchodilator forced vital capacity; PB-FVC6, PB-FVC in six seconds; SD, standard deviation; r, correlation coefficient; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points; PLATINO, COPD in Five Latin American Cities; COSYCONET, COPD and Systemic Consequences-Comorbidities Network; SUMMIT, Study to Understand Mortality and

Morbidity in COPD; UPLIFT, Understanding Potential Long-term Impacts on Function with Tiotropium; CRYSTAL, Effect of Glycopyrronium or Indacaterol Maleate and Glycopyrronium Bromide Fixed-Dose Combination on Symptoms and Health Status in Patients with Moderate COPD; CCQ, Clinical COPD Questionnaire; EQ-5D, European Quality of Life Five Dimensions; CI, confidence interval; B, unstandardized beta; SE, standard error.

Declarations

Ethics Approval and Informed Consent:

The ethics approval for this study was obtained from the Medical Research and Ethics Committee of UMMC (MECID. No 2017814-5496) and the Ministry of Health Malaysia (KKM.NIHSEC/P18-27(5). This study was also registered with the National Medical Research Register (NMRR-17-2549-38621). Written informed consent was obtained from every patient.

Consent for publication:

Not applicable.

Availability of Data and Materials:

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

Competing Interest:

The authors declare no potential conflicts of interest in respect to the research, authorship, and publication of this article.

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Authors Contributions:

CSC, DLCN, MABI, SBT, YKP and CKL contributed to the conception and design of the study; CSC, DLCN, SBM contributed to the data acquisition; CSC, DLCN, SBM, and SBT contributed to the data analysis and interpretation; CSC, DLCN, MABI, SBT, YKP and CKL contributed to the drafting of the article and critically revising it. All authors made final approval of the version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved.

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Figures

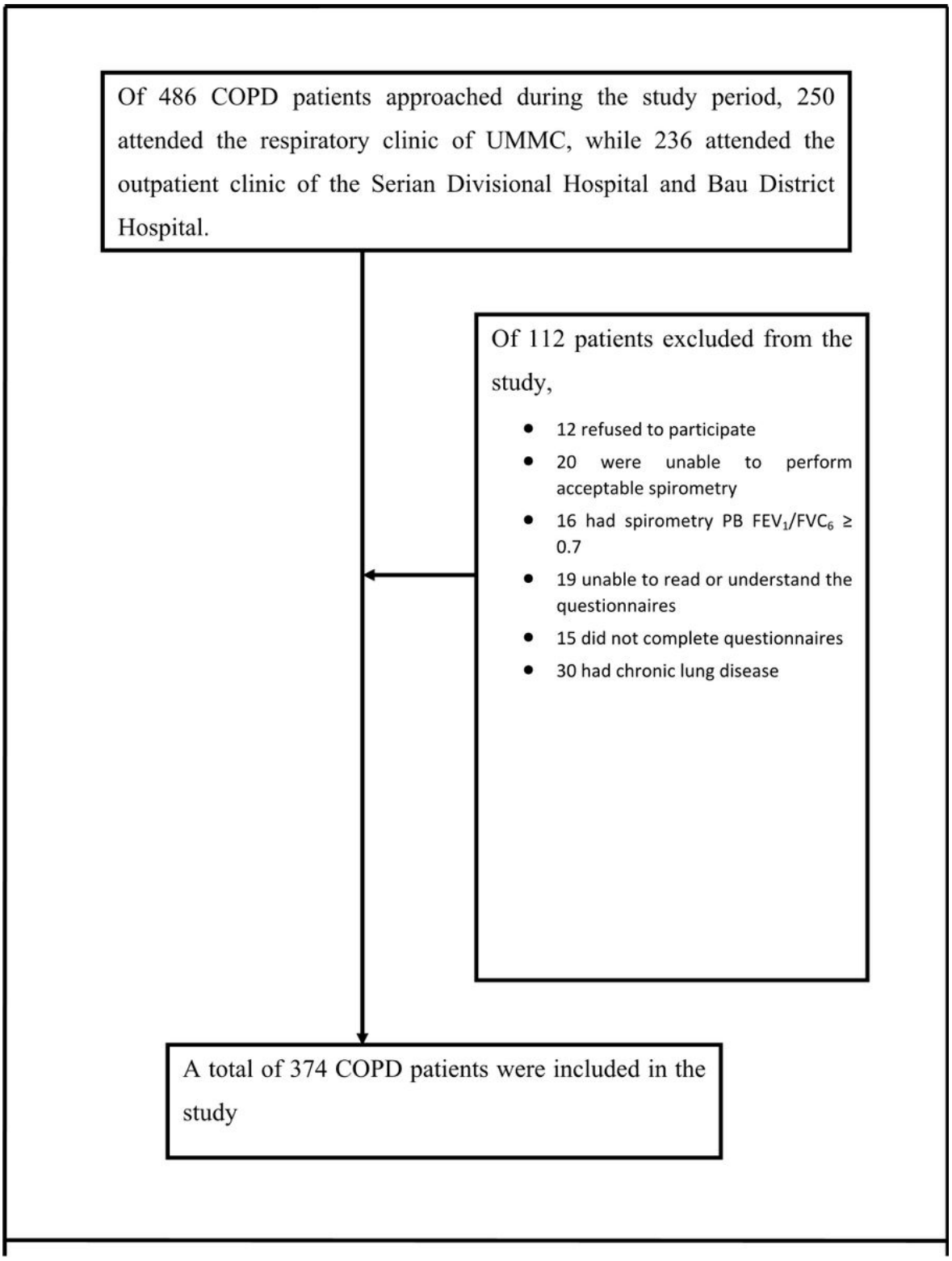

Figure 1

Algorithm of patients' recruitment in the study