

# Clinical phenotypes of COPD and health-related quality of life: a cross-sectional study

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**Introduction:** The Spanish COPD guideline (GesEPOC) classifies COPD into four clinical phenotypes based on the exacerbation frequency and dominant clinical manifestations. In this study, we compared the disease-specific health-related quality of life (HRQoL) of patients with different clinical phenotypes.

**Methods:** This was a cross-sectional study of patients with COPD attending the respiratory medicine clinic of University of Malaya Medical Centre from 1 June 2017 to 31 May 2018. Disease-specific HRQoL was assessed by using the COPD Assessment Test (CAT) and St George's Respiratory Questionnaire for COPD (SGRQ-c).

**Results:** Of 189 patients, 28.6% were of non-exacerbator phenotype (NON-AE), 18.5% were of exacerbator with emphysema phenotype (AE NON-CB), 39.7% were of exacerbator with chronic bronchitis phenotype (AE CB), and 13.2% had asthma-COPD overlap syndrome phenotype (ACOS). The total CAT and SGRQ-c scores were significantly different between the clinical phenotypes ( $P < 0.001$ ). Patients who were AE CB had significantly higher total CAT score than those with ACOS ( $P = 0.033$ ), AE NON-CB ( $P = 0.001$ ), and NON-AE ( $P < 0.001$ ). Concerning SGRQ-c, patients who were AE CB also had a significantly higher total score than those with AE NON-CB ( $P = 0.001$ ) and NON-AE ( $P < 0.001$ ). However, the total SGRQ-c score of AE CB patients was only marginally higher than those who had ACOS ( $P = 0.187$ ). There was a significant difference in the score of each CAT item (except CAT 7) and SGRQ-c components between clinical phenotypes, with AE CB patients recording the highest score in each of them. **Conclusion:** Patients who were AE CB had significantly poorer HRQoL than other clinical phenotypes and recorded the worst score in each of the CAT items and SGRQ-c components. Therefore, AE CB patients may warrant a different treatment approach that focuses on the exacerbation and chronic bronchitis components.

**Keywords:** chronic obstructive pulmonary disease, chronic bronchitis, asthma, clinical phenotypes, health-related quality of life, emphysema, exacerbation

## Introduction

COPD is a common, preventable, and treatable airway disease characterized by persistent respiratory symptoms and airflow limitation, due to abnormal inflammatory response of the airways to noxious particles or gases.<sup>1</sup> It is currently the fourth leading cause of death in the world. It is also expected to become the third leading cause of death, and fifth leading cause of disease burden by 2020.<sup>2,3</sup> The overall prevalence of COPD in the Asia-Pacific region is 6.2%.<sup>4</sup> COPD population represents a substantial socioeconomic burden in these countries as two-fifth of them have work restriction, one-fifth has severe respiratory symptoms, and one-fifth had required hospital admission in the past 12-months because of exacerbation.<sup>4</sup>

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COPD phenotype refers to a single or combination of disease attributes that describe differences between COPD patients based on clinically significant parameters, such as exacerbation, symptoms, response to treatment, rate of disease progression, and mortality.<sup>5</sup> In 2012, the Spanish Society of Pulmonology and Thoracic Surgery published the Spanish COPD guideline (GesEPOC), which was the first clinical guideline that phenotypes COPD patients based on their exacerbation frequency and dominant clinical manifestations, such as bronchitis, emphysema, and bronchial asthma (BA).<sup>6</sup> Even though many existing data report on the health-related quality of life (HRQoL) of COPD patients, studies that compare HRQoL among different clinical phenotypes simultaneously are lacking.

HRQoL is defined as individual satisfaction or happiness with an aspect of their life that is affected by their health either in physical, mental, emotional, or social functioning.<sup>7</sup> Poor HRQoL is associated with increased level of dyspnea, physical impairment, mental health problem, hospital admission, and mortality.<sup>8–10</sup> HRQoL of COPD patients can be measured by using generic questionnaires, such as Short Form Survey-36 and Euro-Qol-5D; or disease-specific questionnaires, such as COPD Assessment Test (CAT), St Georges Respiratory Questionnaire for COPD (SGRQ-c), and Clinical COPD Questionnaire (CCQ).<sup>11,12</sup>

In this study, we aimed to compare the disease-specific HRQoL of patients with COPD attending the University of Malaya Medical Centre (UMMC) based on their clinical phenotype as defined by the GesPOC guideline. UMMC is a tertiary teaching hospital, located in Kuala Lumpur, the capital of Malaysia.

## Methods

### Study design and patients

This is a cross-sectional study of patients with COPD attending the respiratory medicine clinic of UMMC from 1 June 2017 to 31 May 2018. All patients studied were aged  $\geq 40$  years, with the ratio of post-bronchodilator FEV<sub>1</sub> (PB-FEV<sub>1</sub>) over post-bronchodilator FVC of  $< 0.7$ . Patients with concomitant BA were included, but patients with other chronic lung diseases, such as bronchiectasis or interstitial lung disease were excluded. The estimated sample size (n) was 155 patients, calculated based on the reported COPD prevalence of 11.4%, Z <sub>$\alpha$</sub>  of 1.96, and precision of 0.05.<sup>13</sup> This study aimed to determine the impact of different COPD clinical phenotypes on patients' disease-specific HRQoL assessed by using CAT and SGRQ-c. The primary objective was to compare the total

CAT and SGRQ-c score of different clinical phenotypes; while the secondary objective was to compare the score of individual items of CAT and each component of SGRQ-c of different clinical phenotypes. The hospital's ethics committee approved this study. Written informed consent was obtained from all the study patients. This study was conducted in accordance with the Declaration of Helsinki.

### Procedure

Eligible patients were consecutively identified from those attending the respiratory medicine clinic. Demographic and clinical data of these patients were obtained from face-to-face interview and case records.

Patients were categorized as never-smokers if they had smoked  $< 100$  cigarettes in their lifetime; previous smokers if they had smoked  $> 100$  cigarettes in their lifetime and no more smoking; and current smokers if they had smoked  $> 100$  cigarettes in their lifetime and still smoking every day or some of the days.<sup>14</sup> The patients' dyspnea was graded according to the modified Medical Research Council scale that consists of five grades: 0 – no dyspnea except on strenuous activity; 1) dyspnea when walking uphill; 2) walk slower than people with same age due to dyspnea; 3) stops for breath due to dyspnea after walking 100 m at level; and 4) too dyspnoeic to leave home or dyspnea when dressing.<sup>15</sup>

PB-FEV<sub>1</sub> was expressed in % of predicted (PB-FEV<sub>1</sub> %). Total exacerbation only considered the number of moderate and severe exacerbations. A moderate exacerbation was defined as an exacerbation that required outpatient treatment with corticosteroid and/or antibiotic; while severe exacerbation was defined as an exacerbation that needed hospital admission.<sup>16</sup> For patients on COPD treatment, a new episode of exacerbation required at least 4 weeks from the resolution of a previous exacerbation; while for patients not on COPD treatment, a new episode of exacerbation required at least 6 weeks from the last exacerbation.<sup>17</sup> Chronic bronchitis (CB) was defined as a cough with sputum for at least 3 months in a year for 2 consecutive years.<sup>18</sup> In the presence of COPD, BA was defined as those already currently diagnosed with BA or had very definite PB-FEV<sub>1</sub> improvement of  $> 400$  mL and 15%, or blood eosinophil of  $> 300$  cells/mm.<sup>3,19</sup>

The COPD clinical phenotypes were defined according to the GesEPOC guideline.<sup>20</sup> Non-exacerbator phenotype (NON-AE) was defined by the presence of  $< 2$  episodes of moderate exacerbation and without severe exacerbation in the past 1 year. Exacerbator phenotype (AE) was defined by the presence of 2 or more episodes of moderate exacerbation or

an episode of severe exacerbation in the past 1 year. This phenotype was further divided into AE with CB phenotype (AE CB) and AE with emphysema phenotype (AE NON-CB). The former phenotype was defined by the presence of CB; while the latter phenotype was defined by the presence of air-trapping on examination or investigations. Asthma-COPD overlap syndrome phenotype (ACOS) was defined by the presence of BA criteria as mentioned previously without the consideration of the number of exacerbation.

In assessing HRQoL, the patients were instructed to answer the CAT and SGRQ-c questionnaires independently with minimal assistance from the investigators. The patients could choose to answer the original English version, or validated Malay or Chinese version. The CAT questionnaire consists of eight items, namely, cough (CAT 1), phlegm (CAT 2), chest tightness (CAT 3), breathlessness (CAT 4), activity limitation (CAT 5), confidence in leaving home (CAT 6), sleep (CAT 7), and energy (CAT 8).<sup>21</sup> The score for each of these items ranges from 0 to 5 with the total score ranging from 0 to 40. The total CAT score in a healthy subject is  $\leq 6$ , with a higher score reflecting a greater or worse impact of COPD on HRQoL.<sup>22</sup> The SGRQ-c questionnaire consists of 14 questions, with questions 1–7 interrogating the symptom component, questions 9 and 12 concerning activity component, and questions 8, 10, 11, 13, and 14 relating to impact component.<sup>23</sup> The score of each component and the total score range from 0% to 100%, with a higher score reflecting worse HRQoL. In healthy subjects, the score of the total is  $\leq 6\%$ , symptom component is  $\leq 12\%$ , activity component is  $\leq 9\%$ , and impact component is not  $> 2\%$ .<sup>24</sup> CAT is a quick assessment tool, while SGRQ-c is more comprehensive but time-consuming.

## Statistical analyses

In this study, categorical variables were expressed as percentages; while continuous variables were expressed as the mean  $\pm$  SD, median or range depending on the normality of the distribution of the variable. For categorical variables, the difference between clinical phenotypes was compared by using the chi-squared test. An adjusted standardized residual of  $> 2$  was considered as significant in the post hoc analysis. For continuous variables, the difference between clinical phenotypes was compared by using one-way ANOVA test or Kruskal–Wallis  $H$  test, as applicable. The post hoc analysis for the former was the Tukey's test, while for the latter, was the Dunn's procedure with a Bonferroni adjustment. A  $P$ -value of  $< 0.05$  was considered statistically significant. Statistical analyses were performed using the

software package, SPSS for Windows version 23.0 (SPSS Inc., Chicago, IL, USA).

## Results

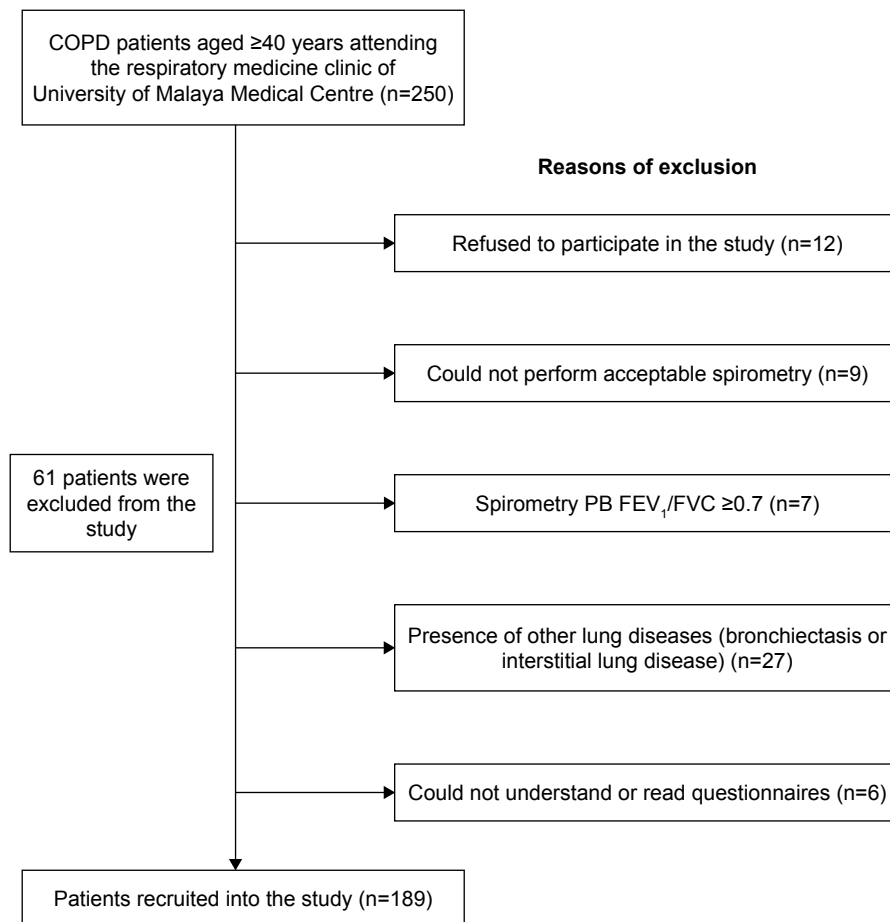
### Demographic and clinical characteristics

A total of 189 patients who met the study criteria were included in the study (Figure 1). Patients' demographic and clinical characteristics are shown in Table 1. A total of 28.6% of patients were of NON-AE, 18.5% were of AE NON-CB, 39.7% were of AE CB, and 13.2% had ACOS. Among patients of NON-AE, 46.3% were of CB and 53.7% were of NON-CB. Regardless of the phenotypes, male patients were predominant and the majority of the patients were ex-smokers. The age, gender proportion, ethnicity distribution, smoking status, and smoking quantity difference among the patients with the different clinical phenotypes were not significant.

The dyspnea symptom ( $P=0.002$ ), PB-FEV<sub>1</sub> % ( $P=0.025$ ), and total exacerbation ( $P<0.001$ ) were significantly different between clinical phenotypes. Patients who were of AE CB had significantly worse dyspnea symptom ( $P=0.002$ ), lower PB-FEV<sub>1</sub> % ( $P=0.018$ ), and higher total number of exacerbations ( $P<0.01$ ) than patients of NON-AE. The total number of exacerbations was also significantly higher in patients who had ACOS ( $P<0.001$ ) and AE NON-CB ( $P<0.001$ ) compared with patients of NON-AE. Despite the total number of exacerbations for patients with ACOS was also higher than that of AE NON-CB ( $3.4\pm 5.2$  vs  $1.9\pm 1.9$ ), this difference was not statistically significant ( $P=0.999$ ).

### HRQoL according to clinical phenotypes

The total CAT and SGRQ-c scores were significantly different between clinical phenotypes (all  $P$ -values  $< 0.001$ ) (Table 2). Patients who were of AE CB had significantly higher total CAT score than those with ACOS ( $23.6\pm 8.0$  vs  $18.3\pm 10.1$ ,  $P=0.033$ ), AE NON-CB ( $23.6\pm 8.0$  vs  $15.8\pm 8.0$ ,  $P=0.001$ ), and NON-AE ( $23.6\pm 8.0$  vs  $18.0\pm 8.0$ ,  $P<0.001$ ). In terms of SGRQ-c, patients who were of AE CB also had significant higher total score than those with AE NON-CB ( $61.5\pm 20.9$  vs  $44.0\pm 21.4$ ,  $P=0.001$ ) and NON-AE ( $61.5\pm 20.9$  vs  $42.6\pm 20.1$ ,  $P<0.001$ ). However, the total SGRQ-c score of patients with AE CB was only marginally higher than those who had ACOS ( $61.5\pm 20.9$  vs  $51.5\pm 25.9$ ,  $P=0.187$ ). Although the total CAT score increased from patients who were of AE NON-CB, to NON-AE, and ACOS; while the total SGRQ-c score increased from patients who were of NON-AE, to AE NON-CB, and ACOS, the differences between these clinical phenotypes were not statistically significant.



**Figure 1** Algorithm of patients' recruitment into the study.

**Abbreviation:** PB- $FEV_1/FVC$ , ratio of post-bronchodilator force expiratory volume in 1 second/forced vital capacity.

There was a significant difference in the score of each CAT items (except CAT 7) and SGRQ-c components between clinical phenotypes (Table 2). Patients with AE CB had the highest score in each of the CAT items and SGRQ-c components (Figures 2 and 3). Patients who had ACOS had the second highest score in each of the SGRQ-c components and CAT 1, CAT 3, CAT 6, and CAT 7. CAT 4 had the highest score regardless of the patients' clinical phenotype.

## Discussion

Regardless of the clinical phenotypes, the HRQoL of our patients was markedly impaired compared with healthy individuals. AE CB was the only clinical phenotype associated with significantly poorer HRQoL. The poor HRQoL was not solely attributable to cough and phlegm symptoms (CAT 1 and 2), which could be confounded by the definition of CB. The sub-analysis of CAT items demonstrated that AE CB was associated with more chest tightness, breathlessness, activity limitation, fear of leaving home, sleep disturbance, and lack

of energy (CAT 3–8). Moreover, sub-analysis of SGRQ-c components also demonstrated that AE CB was associated with more respiratory symptoms and disturbance to daily physical activities as well as psychosocial function. Patients with ACOS appeared to have poorer HRQoL than those with AE NON-CB or NON-AE although the difference was not statistically significant, which could be due to the smaller number of subjects with ACOS. ACOS was associated with more core symptoms of BA, such as a cough, chest tightness, and sleep disturbance, while daily activities and energy were less affected. Surprisingly, the HRQoL of patients with AE NON-CB was not markedly worse than those with NON-AE. Such a finding suggests that higher exacerbation frequency alone without an unfavorable clinical manifestations might not be sufficient to have a detrimental effect on patients' HRQoL. The clinical manifestation that was associated with the poorest HRQoL was CB, followed by BA and NON-CB.

From this study, we can conclude that HRQoL is significantly worse in patients with AE CB and numerically

**Table 1** Demographic and clinical characteristics of COPD patients according to their clinical phenotypes

Characteristics	COPD phenotype (n, %)				P-value
	NON-AE 54 (28.6)	AE NON-CB 35 (18.5)	AE CB 75 (39.7)	ACOS 25 (13.2)	
Age (years, mean $\pm$ SD)	74.1 $\pm$ 8.1	72.7 $\pm$ 8.7	70.7 $\pm$ 9.2	70.0 $\pm$ 13.1	0.151
Gender (n, %)					
Male	50 (92.6)	32 (91.4)	70 (93.3)	23 (92.0)	0.986
Female	4 (7.4)	3 (8.6)	5 (6.7)	2 (8.0)	
Ethnicity (n, %)					
Malay	19 (35.2)	12 (34.3)	32 (42.7)	10 (40.0)	0.734
Chinese	27 (50.0)	18 (51.4)	30 (40.0)	9 (36.0)	
Indian	8 (14.8)	5 (14.3)	13 (17.3)	6 (24.0)	
Smoking status (n, %)					
Never smoker	2 (3.7)	3 (8.6)	4 (5.3)	3 (12.0)	0.348
Previous	40 (74.1)	19 (54.3)	55 (73.3)	15 (60.0)	0.601
Current	12 (22.2)	13 (37.1)	16 (21.3)	7 (28.0)	
Quantity of cigarettes smoked (pack-years, mean)	42.3 $\pm$ 30.4	44.6 $\pm$ 30.1	43.9 $\pm$ 27.9	39.0 $\pm$ 35.4	
Dyspnea (mean $\pm$ SD; 95% CI)	1.8 $\pm$ 1.3; 1.5–2.2	2.0 $\pm$ 1.2; 1.6–2.4	2.7 $\pm$ 1.1; 2.4–2.9	2.2 $\pm$ 1.4; 1.6–2.8	0.002
PB-FEV <sub>1</sub> (%; mean $\pm$ SD; 95% CI)	57.8 $\pm$ 20.2; 52.3–63.4	51.1 $\pm$ 23.1; 43.2–59.0	48.2 $\pm$ 23.6; 42.8–53.7	52.8 $\pm$ 16.2; 46.1–59.5	0.025
Exacerbations (mean $\pm$ SD; 95% CI)					
Total	0.5 $\pm$ 1.8; 0.1–1.0	1.9 $\pm$ 1.9; 1.3–2.6	4.8 $\pm$ 6.8; 3.2–6.4	3.4 $\pm$ 5.2; 1.3–5.6	<0.001
Moderate	0.4 $\pm$ 1.3; 0.1–0.8	0.7 $\pm$ 1.0; 0.4–1.1	2.9 $\pm$ 5.4; 1.7–4.2	1.9 $\pm$ 3.2; 0.6–3.3	<0.001
Severe	0	1.3 $\pm$ 1.2; 0.9–1.7	1.9 $\pm$ 2.1; 1.4–2.4	1.5 $\pm$ 2.5; 0.5–2.6	<0.001

**Abbreviations:** ACOS, asthma-COPD overlap syndrome phenotype; AE CB, exacerbator with chronic bronchitis phenotype; AE NON-CB, exacerbator with emphysema phenotype; NON-AE, non-exacerbator phenotype; PB-FEV<sub>1</sub>, post-bronchodilator forced expiratory volume in 1 second.

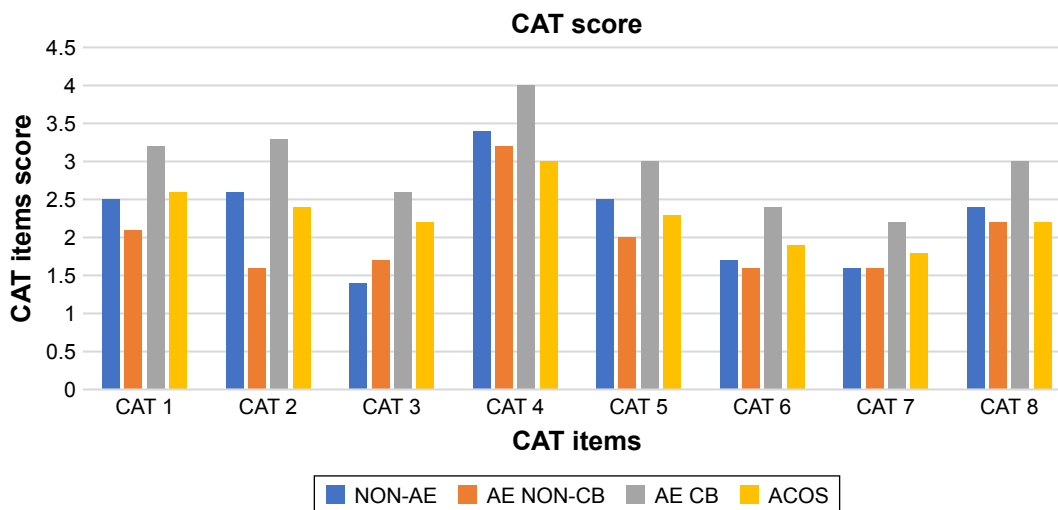
worse in patients with ACOS compared with patients with AE NON-CB, and least affected in patients with NON-AE. These findings agree with the result of earlier studies. In the COPD History Assessment in Spain study, Cosio et al

reported a significant higher CAT score in patients with AE CB ( $P < 0.001$ ), and the CAT score was numerically higher in those with ACOS followed by those with AE NON-CB and NON-AE.<sup>25</sup> In another multicenter observational study in

**Table 2** CAT and SGRQ-c scores of COPD patients according to their clinical phenotypes

Parameters	COPD phenotype				P-value
	NON-AE	AE NON-CB	AE CB	ACOS	
CAT score (mean $\pm$ SD; 95% CI)					
Total	18.0 $\pm$ 8.0; 15.8–20.2	15.8 $\pm$ 8.0; 13.1–18.6	23.6 $\pm$ 8.0; 21.8–25.4	18.3 $\pm$ 10.1; 14.0–22.7	<0.001
Cough (CAT 1)	2.5 $\pm$ 1.2; 2.1–2.8	2.1 $\pm$ 1.3; 1.6–2.5	3.2 $\pm$ 1.2; 2.9–3.5	2.6 $\pm$ 1.6; 2.0–3.3	<0.001
Phlegm (CAT 2)	2.6 $\pm$ 1.8; 2.1–3.0	1.6 $\pm$ 1.6; 1.0–2.1	3.3 $\pm$ 1.7; 2.9–3.7	2.4 $\pm$ 1.9; 1.6–3.2	<0.001
Chest tightness (CAT 3)	1.4 $\pm$ 1.7; 0.9–1.8	1.7 $\pm$ 1.5; 1.2–2.2	2.6 $\pm$ 1.6; 2.2–2.9	2.2 $\pm$ 1.7; 1.5–2.9	<0.001
Breathlessness (CAT 4)	3.4 $\pm$ 1.7; 3.0–3.9	3.2 $\pm$ 1.5; 2.7–3.7	4.0 $\pm$ 1.3; 3.7–4.2	3.0 $\pm$ 1.7; 2.3–3.7	0.020
Activity limitation (CAT 5)	2.5 $\pm$ 1.8; 2.0–3.0	2.0 $\pm$ 1.7; 1.4–2.6	3.0 $\pm$ 1.6; 2.6–3.4	2.3 $\pm$ 1.9; 1.5–3.1	0.038
Confidence in leaving home (CAT 6)	1.7 $\pm$ 1.9; 1.2–2.2	1.6 $\pm$ 1.8; 1.0–2.2	2.4 $\pm$ 1.6; 2.1–2.8	1.9 $\pm$ 1.9; 1.1–2.7	0.022
Sleep (CAT 7)	1.6 $\pm$ 1.6; 1.2–2.1	1.6 $\pm$ 1.6; 1.0–2.1	2.2 $\pm$ 1.6; 1.8–2.5	1.8 $\pm$ 1.8; 1.1–2.5	0.127
Energy (CAT 8)	2.4 $\pm$ 1.1; 2.1–2.7	2.2 $\pm$ 1.5; 1.7–2.7	3.0 $\pm$ 1.4; 2.7–3.4	2.2 $\pm$ 1.6; 1.5–2.8	0.004
SGRQ-c score, % (mean $\pm$ SD; 95% CI)					
Total	42.6 $\pm$ 20.1; 37.1–48.1	44.0 $\pm$ 21.4; 36.6–51.4	61.5 $\pm$ 20.9; 56.7–66.3	51.5 $\pm$ 25.9; 40.8–62.2	<0.001
Symptoms	36.8 $\pm$ 19.9; 31.4–42.3	43.3 $\pm$ 23.6; 35.3–51.5	61.7 $\pm$ 20.4; 57.0–66.4	59.2 $\pm$ 25.1; 48.9–69.6	<0.001
Activities	48.9 $\pm$ 32.5; 40.1–57.8	56.8 $\pm$ 27.8; 47.3–66.4	70.5 $\pm$ 25.1; 64.7–76.2	58.0 $\pm$ 34.6; 43.8–72.3	0.001
Impact	40.9 $\pm$ 20.1; 35.4–46.3	36.9 $\pm$ 24.8; 28.4–45.5	56.0 $\pm$ 27.2; 49.8–62.3	44.8 $\pm$ 32.1; 31.2–58.1	0.001

**Abbreviations:** ACOS, asthma-COPD overlap syndrome phenotype; AE CB, exacerbator with chronic bronchitis phenotype; AE NON-CB, exacerbator with emphysema phenotype; CAT, COPD Assessment Test; NON-AE, non-exacerbator phenotype; SGRQ-c, St Georges Respiratory Questionnaire for COPD.



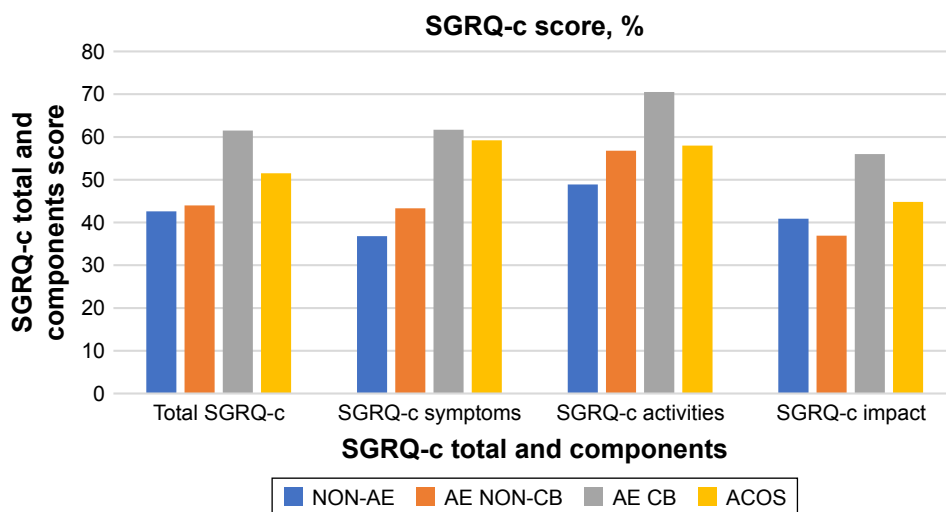
**Figure 2** Score of CAT items according to COPD clinical phenotypes.

**Abbreviations:** ACOS, asthma-COPD overlap syndrome phenotype; AE CB, exacerbator with chronic bronchitis phenotype; AE NON-CB, exacerbator with emphysema phenotype; CAT, COPD Assessment Test; NON-AE, non-exacerbator phenotype.

Spain, Miravittles et al also reported a significant higher CAT score in patients with AE CB ( $P < 0.001$ ).<sup>26</sup> Those with ACOS and AE NON-CB had an intermediate score, while patients of NON-AE had the lowest score. A study by Corlateanu et al, however, reported that the CAT, SRGQ, and CCQ scores were significantly higher in frequent exacerbators; and those with AE NON-CB recording the highest values in each of the parameters.<sup>27</sup> In short, the present study and available data consistently highlight that patients with NON-AE had the best HRQoL, while patients with frequent exacerbations, particularly of the AE CB phenotype had the worst HRQoL. Our study further complements these existing works by demonstrating

that AE CB phenotype is indeed associated with the worst score in each of the CAT items and SGRQ-c components.

In this study, the higher exacerbation frequency and active inflammation of CB led to poorer HRQoL in patients with the AE CB phenotype. Frequent exacerbation has been known to have a profound impact on HRQoL. Seemungal et al reported that patients with three or more exacerbations per year had significant worse SGRQ score ( $P < 0.001$ ), while Mackay et al reported that patients with two or more exacerbations per year had significantly worse CAT score ( $P = 0.025$ ).<sup>28,29</sup> Similarly, CB was reported to be independently associated with poorer HRQoL compared with



**Figure 3** Total and component scores of SGRQ-c according to COPD clinical phenotypes.

**Abbreviations:** ACOS, asthma-COPD overlap syndrome phenotype; AE CB, exacerbator with chronic bronchitis phenotype; AE NON-CB, exacerbator with emphysema phenotype; NON-AE, non-exacerbator phenotype; SGRQ-c, St Georges Respiratory Questionnaire for COPD.

without CB in several recent studies. In the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints and Genetic Epidemiology of COPD (COPDGene) studies, Agusti et al and Kim et al reported a significantly worse SGRQ score in CB patients (all  $P < 0.001$ ); while in the Korea COPD Subgroup Study Team, Choi et al reported significantly worse CAT ( $P < 0.001$ ) and SGRQ ( $P < 0.001$ ) scores in the CB group.<sup>30–32</sup> de Oca et al also reported significantly poorer respiratory symptoms, including dyspnea ( $P = 0.002$ ) and wheezing ( $P = 0.003$ ) as well as general HRQoL ( $P = 0.049$ ) measured by Short Form-12 among CB patients of the COPD in five Latin America Cities study.<sup>33</sup> In comparison with NON-CB, the airway inflammation of COPD that is mediated by neutrophil, macrophage, and CD8<sup>+</sup> lymphocyte is more aggressive in CB leading to more mucus production and small airway obstruction, which explains the worse HRQoL.<sup>34</sup> In the COPDGene and Epidemiologic Study of COPD in Spain study, Hardin et al and Miravittles et al, reported significantly worse SGRQ in patients of ACOS ( $P = 0.009$  and  $P < 0.001$ , respectively).<sup>35,36</sup> The number of subjects of ACOS in both of these studies were much more than ours ( $n = 119$  and  $n = 67$ ) and, therefore, both these studies were able to show significantly worse HRQoL in patients of ACOS. In ACOS, the dual inflammatory processes of COPD and BA mediated by eosinophils, mast cells, and CD4<sup>+</sup> lymphocytes led to poorer HRQoL.<sup>37</sup>

The present study findings support the importance of phenotyping COPD based on exacerbation frequency and dominant clinical manifestations according to GesEPOC guideline to allow a more personalized treatment. Patients with AE CB may warrant a different treatment approach that focuses on the exacerbation and CB components because they have the poorest HRQoL. Treatment with azithromycin to reduce exacerbation frequency and roflumilast to control CB symptoms should be added early in patients with this phenotype, especially when long-acting beta 2-agonist and long-acting muscarinic antagonist fail to control the COPD symptoms.<sup>20</sup> In order to preserve the HRQoL in ACOS, inhaled corticosteroid that controls the BA component should be initiated upon diagnosis. Besides, other non-pharmacological therapy, such as smoking cessation, pulmonary rehabilitation, and nutritional support should be offered early to improve respiratory symptoms and HRQoL.

To our knowledge, this is the first study in the Asia-Pacific region that compares the HRQoL of all the COPD clinical phenotypes simultaneously. Different

disease-specific HRQoL assessment tools were utilized to obtain more representative results. The impact of COPD clinical phenotypes on each of the individual CAT items and SGRQ-c components was also analyzed.

This study has several limitations. First, it was performed in a single center, thus limiting the generalizability of the results. Second, there is the possibility of misclassification of the clinical phenotypes because the exacerbation frequency was subjected to the recall error of the patients. We tried to minimize this error by double checking the exacerbation history from patients' available medical records. Finally, the number of ACOS patients was disproportionately small for statistically significant differences to be achieved when comparison of HRQoL was made with the other phenotypes.

## Conclusion

This study concluded that patients who were AE CB had significant poorer HRQoL than other clinical phenotypes. It further complements existing studies by demonstrating that patients of AE CB also had the worst score in each of the CAT items and SGRQ-c components. Therefore, patients of AE CB may warrant a different treatment approach that focuses on the exacerbation and CB components. Phenotyping COPD patients based on exacerbation frequency and dominant clinical manifestations are essential to achieving a more directed treatment.

## Ethics approval and informed consent

The UMMC Hospital's ethics committee approved this study (reference MECID.No 2017814-5496). Informed consent was obtained from all the study patients.

## Data availability

The study data will be shared on request due to patients' confidentiality and can be obtained from the corresponding author.

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## Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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