Clinical Phenotypes and Heath-Related Quality of Life of COPD Patients in a Rural Setting in Malaysia – A Cross-Sectional Study

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Abstract

Background:

The Spanish chronic obstructive pulmonary disease (COPD) guideline phenotypes patients according to the exacerbation frequency and COPD subtypes. In this study, we compared the patients’ health-related quality of life (HRQoL) according to their COPD phenotypes.

Methods:

This was a cross-sectional study of COPD patients who attended the outpatient clinic of the Serian Divisional Hospital and Bau District Hospital from 23rd January 2018 to 22nd January 2019. The HRQoL was assessed using modified Medical Research Council (mMRC), COPD Assessment Test (CAT), and St George’s Respiratory Questionnaire for COPD (SGRQ-c).

Results:

Of 185 patients, 108 (58.4%) were non-exacerbators (NON-AE), 51 (27.6%) were frequent exacerbators (AE), and the remaining 26 (14.1%) had asthma-COPD overlap (ACO). Of AE patients, 42 (82.4%) had chronic bronchitis and only 9 (17.6%) had emphysema. Of the COPD patients, 65.9% had exposure to biomass fuel and 69.1% were ex- or current smokers.

The scores of mMRC, CAT, and SGRQ-c were significantly different between COPD phenotypes (p < 0.001). There were significantly more patients with mMRC 2 – 4 among AE (68.6%) (p < 0.001), compared to those with ACO (38.5%) and NON-AE (16.7%). AE patients had significantly higher total CAT (p = 0.003; p < 0.001) and SGRQ-c (both p < 0.001) scores than those with ACO and NON-AE. Patients with ACO also had significantly higher total CAT and SGRQ-c (both p < 0.001) scores than those with NON-AE.

AE patients had significantly higher score in each item of CAT and component of SGRQ-c compared to those with NON-AE (all p < 0.001), and ACO [(p = 0.003 – 0.016; p = < 0.001 – 0.005) except CAT 1, 2 and 7. ACO patients had significantly higher score in each item of CAT and component of SGRQ-c (p = < 0.001 – 0.040; p < 0.001) except CAT 2 and activity components of SGRQ-c.

Conclusions:

The HRQoL of COPD patients was significantly different across COPD phenotypes. HRQoL was worst in AE, followed by ACO and NON-AE. This study supports phenotyping COPD patients based on their exacerbation frequency and COPD subtypes. The treatment of COPD should be personalised according to these two factors.

Background:
Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable airway disease characterized by persistent respiratory symptoms and airflow limitation, due to inflammatory response of the airway and lung tissue to noxious particles or gases. Worldwide, COPD is currently the fourth leading cause of death and is expected to rank number three by 2030. It also ranks second in the disease burden measured by the disability-adjusted life-years, causing substantial socioeconomic burden in many countries.

COPD phenotype is defined as a single or combination of disease attributes that describe the differences between individuals with COPD according to their clinically meaningful outcomes, such as exacerbation, symptoms, rate of disease progression, response to therapy, and mortality risk. In 1989, Snider proposed to divide COPD into “chronic bronchitis”, “emphysema”, and “asthmatic” subtypes. In 2012, the Spanish Society of Pulmonology and Thoracic Surgery proposed to phenotype COPD based on the exacerbation frequency and existing COPD subtypes.

Health-related quality of life (HRQoL) is defined as an individual's happiness or satisfaction with an aspect of his/her life which is affected by physical, mental, emotional and social health. Impaired HRQoL is common in COPD patients due to the troublesome respiratory symptoms, limited physical activity, psychological distress, sleep disturbance and concomitant co-morbidities. While there have been many studies to determine the impact of COPD on the patients’ HRQoL, studies that specifically compare HRQoL across different COPD phenotypes are limited, particularly in Asian countries and in the rural setting.

Methods:

Study Design and Patients:

We conducted a cross-sectional study on patients with COPD attending the outpatient clinic of the Serian Divisional Hospital and Bau District Hospital from 23th January 2018 to 22th January 2019. Both hospitals are primary care centres that serve the rural population of southern Sarawak, a state of Malaysia in northern Borneo Island. All patients were aged 35 years and above, with post-bronchodilator forced expiratory volume in one second (PB-FEV$_1$) over post-bronchodilator forced vital capacity in six seconds (FVC$_6$) of < 0.7. Patients with clinical or radiological diagnosis of other chronic lung diseases (such as bronchiectasis and interstitial lung disease), active tuberculosis and lung tumours were excluded. The estimated minimum sample size for the study was 140 based on the prevalence of 10.1% in previous study at 5% of Type-1 error and 5% of precision. The primary objective of this study was to compare the modified Medical Research Council (mMRC) score, total COPD Assessment Tool (CAT) score and total St George’s Respiratory Questionnaire COPD (SGRQ-c) score of different COPD phenotypes. The score of each item of CAT and each component of SGRQ-c of different COPD phenotypes were compared as a secondary objective. Written consent was obtained from every patient. Ethics approval was obtained from the Medical Research and Ethics Committee of the National Medical
Research Registry of Malaysia (NMRR-17-2549-38621) and the respective hospitals. The study was conducted in accordance to the Declaration of Helsinki.

**Procedure:**

We consecutively identified eligible patients from the outpatient clinics of both hospitals. Patient demographic and clinical data were acquired from face-to-face interview and the case notes.

Never-smokers were individuals who had smoked < 100 cigarettes in their lifetime. Ex-smoker and current-smoker were defined as those who smoked ≥ 100 cigarettes in their lifetime, the former had quit smoking for a year at the time of interview. Biomass exposure was defined as exposure to biomass smoke from the burning of wood or charcoal for ≥ 100 hours per year. PB-FEV$_1$ was expressed in percent of predicted based on the patients’ age, gender, height, and ethnicity (PB-FEV$_1$ %). A severe exacerbation was defined as an exacerbation that required hospital admission, while a moderate exacerbation was defined as an exacerbation that required outpatient treatment with corticosteroids and/or antibiotic. Total number of exacerbations in this study only included severe and moderate exacerbations, which were associated with increased risk of future exacerbations. The phenotypes of COPD were defined according to the Spanish COPD guideline (GesEPOC) 2017. A non-exacerbator phenotype (NON-AE) was defined as having no severe exacerbation and ≤ one episode of moderate exacerbation in the past one year. Exacerbator phenotype (AE) was defined as having any severe exacerbation or ≥ two episodes of moderate exacerbations in the past one year. AE was further divided into chronic bronchitis (AE-CB) and emphysema (AE NON-CB). The former was defined by presence of cough and sputum for ≥ three months in a year for two consecutive years; while the latter was defined by the presence of air-trapping on examination or investigations. Asthma-COPD overlap phenotype (ACO) included patients who had previously been diagnosed as bronchial asthma (BA); or had PB-FEV$_1$ ≥ 15% and ≥ 400 ml improvement; or blood eosinophil ≥ 300 cells/mm.$^3$. The patients’ HRQoL was assessed using mMRC, CAT and SGRQ-c questionnaires. Patients answered these questionnaires independently in original English version, or validated Malay/Chinese version. They could obtain explanation from the investigators if there was any problem with understanding the questionnaires. mMRC only measured the severity of dyspnea: no dyspnea except on strenuous activity – 0; dyspnea when walking uphill – 1; walked slower than people of the same age because of dyspnea – 2; dyspnea after walking 100 meter on level ground and needed to stop for breath – 3; and dyspnea when dressing or too dyspnoeic to leave home – 4. (mMRC 0–1 was defined as low symptom, while 2–4 was defined as high symptom.) Eight items, each with score ranging 0–5 were measured in the CAT questionnaire. These included cough – CAT 1; sputum – CAT 2; chest tightness – CAT 3; dyspnea – CAT 4; activity limitation – CAT 5; confidence to leave home – CAT 6; sleep – CAT 7; and energy - CAT 8. The total CAT score in normal individuals is ≤ 6. The SGRQ-c questionnaire consisted of three components, in which the symptoms component consists of questions 1–7; activity component consists of questions 9 and 12; and impact component consists of questions 8, 10, 11, 13 and 14. (The total score of SGRQ-c, as well as score of each component range 0 -100%. The SGRQ-c score for normal
individuals is $\leq 6\%$; symptoms component $\leq 12\%$; activity component $\leq 9\%$; and impact components $\leq 2\%$.\(^{(23)}\) For all questionnaires, higher scores denote poorer HRQoL.

**Statistical analysis**

Categorical variables were presented as percentages. The difference between clinical phenotypes was compared using the chi-squared test, with post-hoc analysis taking adjusted standardized residual of $>2$ as significant. Continuous variables were presented as the mean ± standard deviation (SD), or median with inter-quantile range. Differences between clinical phenotypes were compared using one-way ANOVA test or Kruskall-Wallis H test. The post-hoc analysis was Tukey test, or Dunn's procedure with a Bonferroni adjustment, respectively. The significant p-value in this study was $<0.05$. Statistical analyses were performed using the software package, Statistical Package for the Social Sciences (SPSS for Windows version 23.0, SPSS Inc., Chicago, IL, USA).

**Results:**

Demographic and clinical characteristics
We included 185 patients in this study (Fig. 1). Their demographic and clinical characteristics are described in Table 1. Patients were predominantly male, natives of Sarawak, current or ex-smoker and had biomass fuel exposure.
| Characteristic                  | No. of patients, n (185) | COPD phenotype, n (%) | p-value |
|-------------------------------|--------------------------|-----------------------|---------|
|                               |                          | NON-AE (58.4)         | ACO (14.1) | AE (27.6) |         |
| Age, years (mean SD, 95% CI) | 62.5                     | 60.5 11.6; 58.3–62.7 | 60.5 14.0; 54.9–66.2 | 67.9 10.0; 65.1–70.7 | 0.001 |
| Gender, n (%)                 |                          |                       |         |         |         |
| Male                          | 142 (76.8)               | 83 (76.9)             | 15 (57.7) | 44 (86.3) | 0.019 |
| Female                        | 43 (23.2)                | 25 (23.1)             | 11 (42.3) | 7 (13.7)  |         |
| Ethnicity, n (%)              |                          |                       |         |         |         |
| Malay                         | 31 (16.8)                | 12 (11.1)             | 6 (23.1)  | 13 (25.5) | 0.161 |
| Chinese                       | 20 (10.8)                | 14 (13.0)             | 2 (7.7)   | 4 (7.8)   |         |
| Native                        | 134 (72.4)               | 82 (75.9)             | 18 (69.2) | 34 (66.7) |         |
| Smoking status, n (%)         |                          |                       |         |         |         |
| Never smoker                  | 57 (30.9)                | 35 (32.4)             | 11 (42.3) | 11 (21.6) | 0.151 |
| Ex- or current smoker         | 128 (69.1)               | 73 (67.6)             | 15 (57.7) | 40 (78.4) |         |
| Biomass fuel exposure, n (%)  |                          |                       |         |         |         |
| No                            | 122 (65.9)               | 74 (68.5)             | 19 (73.1) | 29 (56.9) |         |
| Yes                           | 63 (34.1)                | 34 (31.5)             | 7 (26.9)  | 22 (43.1) | 0.249 |

Abbreviation: COPD, chronic obstructive pulmonary disease; NON-AE, non-exacerbators; ACO, asthma-COPD overlap; AE, frequent exacerbators; PB-FEV\(_1\), post bronchodilator forced expiratory volume in 1 second; SD, standard deviation; 95% CI, 95% confidence interval

p-values with bold are significant
| Characteristic                  | No. of patients, n | COPD phenotype, n (%) | p-value |
|-------------------------------|-------------------|-----------------------|---------|
|                               | 185               |                       |         |
|                               |                   | NON-AE  | ACO  | AE  |
| Risk for COPD, n (%)          | 63 (34.1)         | 34 (31.5) | 7 (26.9) | 22 (43.1) | 0.430 |
|                               | 49 (26.5)         | 31 (28.7) | 10 (38.5) | 8 (15.7) |
| Cigarette smoking             | 73 (39.4)         | 43 (39.8) | 9 (34.6) | 21 (41.2) |
| Biomass fuel exposure         |                   |                       |         |
| Both                          |                   |                       |         |
| Smoking intensity, pack-years | 17.1              | 14.3   | 14.2; 11.6–17.0 | 18.1   | 19.6; 10.2–26.0 | 22.5   | 19.5; 17.0–28.0 | 0.016 |
| (mean SD, 95% CI)             |                   | 14.2; 11.6–17.0      | 18.1   | 19.6; 10.2–26.0 | 22.5   | 19.5; 17.0–28.0 |
| PB- FEV\textsubscript{1}, %    | 42.8              | 43.6   | 20.1; 39.8–47.4 | 44.4   | 17.9; 37.2–51.7 | 40.4   | 19.3; 34.9–45.8 | 0.566 |
| (mean SD, 95% CI)             |                   | 43.6   | 20.1; 39.8–47.4 | 44.4   | 17.9; 37.2–51.7 | 40.4   | 19.3; 34.9–45.8 |
| Exacerbation episodes, episode |                   |                       | <0.001 |
| (mean SD, 95% CI)             |                   |                       |         |
| Total                         | 1.4               | 0.2   | 0.4; 0.1–0.3 | 0.2   | 0.4; 0.1–0.4 | 4.7   | 3.4; 3.8–5.7 | <0.001 |
|                               | 1.0–1.8           | 0.2   | 0.4; 0.1–0.3 | 0.2   | 0.4; 0.1–0.4 | 4.7   | 3.4; 3.8–5.7 |
| Moderate                      | 1.1               | 0.2   | 0.4; 0.1–0.3 | 0.2   | 0.4; 0.1–0.4 | 3.6   | 2.9; 2.8–4.4 | <0.001 |

Abbreviation: COPD, chronic obstructive pulmonary disease; NON-AE, non-exacerbators; ACO, asthma-COPD overlap; AE, frequent exacerbators; PB- FEV\textsubscript{1}, post bronchodilator forced expiratory volume in 1 second; SD, standard deviation; 95% CI, 95% confidence interval

p-values with bold are significant
| Characteristic | No. of patients, n | COPD phenotype, n (%) | p-value |
|----------------|--------------------|-----------------------|---------|
|                | 185                | NON-AE 108 (58.4)     |         |
|                |                    | ACO 26 (14.1)         |         |
|                |                    | AE 51 (27.6)          |         |
| Severe         | 0.3                | 0                     | 0.3     |
|                |                    | 0                     | 1.1     |
|                |                    | 1.2; 0.8–1.1          | < 0.001 |
|                |                    | 1.5                   |         |

Abbreviation: COPD, chronic obstructive pulmonary disease; NON-AE, non-exacerbators; ACO, asthma-COPD overlap; AE, frequent exacerbators; PB-FEV₁, post bronchodilator forced expiratory volume in 1 second; SD, standard deviation; 95% CI, 95% confidence interval

p-values with bold are significant

### Table 1. Demographic and clinical characteristics of 185 patients according to COPD phenotypes

One hundred and eight (58.4%) patients belonged to the NON-AE phenotype, 51 (27.6%) patients were AE phenotype, and the remaining 26 (14.1%) patients had ACO. Of AE patients, 42 (82.4%) had chronic bronchitis and only 9 (17.6%) had lung emphysema. AE patients were significantly older than those with ACO (67.9 ±10.0 versus 60.5 ±14.0 years, p = 0.024) or NON-AE (67.9 ±10.0 versus 60.5 ±11.6 years, p = 0.001). The smoking intensity in terms of pack-years of AE patients was significantly higher than those with NON-AE (22.5 ±19.5 versus 14.3 ±14.2 pack years, p = 0.012), but not ACO patients. There were significantly more female patients with ACO (42.3%) compared to AE (13.7%) or NON-AE (23.1%) (p = 0.019). The total exacerbation episodes of patients with ACO were significantly lower than that of AE (0.2 ±0.4 versus 4.7 ±3.4, p < 0.001). Otherwise, there was no significant difference in ethnicity, smoking status, biomass exposure, and PB-FEV₁ between the COPD phenotypes.

The scores of mMRC, CAT, and SGRQ-c were significantly different across COPD phenotypes (all p < 0.001) (Table 2). There were significantly more patients with mMRC 2–4 among AE (68.6%), compared to those with ACO (38.5%) and NON-AE (16.7%). Patients with AE had significantly higher total CAT and SGRQ-c scores than those with ACO (17.3 ±9.5 versus 11.7 ±8.6, p = 0.003; 53.5 ±22.7% versus 34.4 ±19.5%, p < 0.001) and NON-AE (17.3 ±9.5 versus 5.5 ±4.7, p < 0.001; 53.5 ±22.7% versus 16.4 ±14.8%, p < 0.001). Patients with ACO also had significantly higher total CAT and SGRQ-c scores than those with NON-AE (11.7 ±8.6 versus 5.5 ±4.7, p < 0.001; 34.4 ±19.5% versus 16.4 ±14.8%, p < 0.001).
Table 2
mMRC, CAT and SGRQ-c scores of COPD patients according to their COPD phenotypes

| Quality of Life Measurement | Clinical Phenotype, n (%) | NON-AE 108 (58.4) | ACO 26 (14.1) | AE 51 (27.6) | p-value |
|-----------------------------|---------------------------|-------------------|---------------|--------------|---------|
| mMRC, n, (%)                |                           |                   |               |              | <0.001  |
| 0–1                         | 90 (83.3)                 | 16 (61.5)         | 16 (31.4)     |              |         |
| 2–4                         | 18 (16.7)                 | 10 (38.5)         | 35 (68.6)     |              |         |
| CAT, score (mean SD, 95% CI)|                           |                   |               |              |         |
| Total                       | 5.5 4.7;                  | 11.7 8.6;         | 17.3 9.5;     | <0.001       |
|                            | 4.6–6.4                   | 8.2–15.2          | 14.6–19.9     |             |
| Cough                       | 1.9 1.3;                  | 2.6 1.1;          | 3.2 1.5;      | <0.001       |
|                            | 1.7–2.2                   | 2.2–3.1           | 2.8–3.6       |             |
| Mucus                       | 1.3 1.2;                  | 1.9 1.5;          | 2.5 1.6;      | <0.001       |
|                            | 1.0–1.5                   | 1.3–2.5           | 2.1–3.0       |             |
| Chest tightness             | 0.4 0.7;                  | 1.4 1.4;          | 2.2 1.4;      | <0.001       |
|                            | 0.3–0.5                   | 0.9–2.0           | 1.9–2.6       |             |
| Walk uphill                 | 0.9 1.1;                  | 1.8 1.3;          | 2.7 1.5;      | <0.001       |
|                            | 0.7–1.1                   | 1.3–2.3           | 2.3–3.1       |             |
| Home activity               | 0.3 0.7;                  | 1.2 1.5;          | 2.0 1.6;      | <0.001       |
|                            | 0.2–0.5                   | 0.6–1.8           | 1.5–2.4       |             |

Abbreviation: COPD, chronic obstructive pulmonary disease; NON-AE, non-exacerbators; ACO, asthma-COPD overlap; AE, frequent exacerbators; mMRC, modified Medical Research Council; CAT, COPD Assessment Test; SGRQ-c, St George’s Respiratory Questionnaire COPD; SD, standard deviation; 95% CI, 95% confidence interval

p-values with bold are significant
| Quality of Life Measurement | Clinical Phenotype, n (%) | NON-AE | ACO | AE | p-value |
|-----------------------------|---------------------------|-------|-----|----|---------|
|                            |                           | 108 (58.4) | 26 (14.1) | 51 (27.6) |         |
| Leaving home                |                           | 0.2 0.6; 0.1–0.3 | 0.9 1.1; 0.4–1.3 | 1.7 1.5; 1.2–2.1 | <0.001 |
| Sleep                       |                           | 0.2 0.6; 0.1–0.3 | 0.9 1.2; 0.4–1.4 | 1.2 1.2; 0.9–1.6 | <0.001 |
| Energy                      |                           | 0.3 0.6; 0.2–0.4 | 1.0 1.4; 0.5–1.6 | 1.8 1.5; 1.2–2.2 | <0.001 |

| SGRQ-c, % (mean SD, 95% CI) |                           | Total | Symptoms | Activities | Impact |
|-----------------------------|---------------------------|-------|----------|------------|--------|
|                            |                           | 16.4 14.8; 13.5–19.2 | 18.3 14.3; 15.5–21.0 | 27.1 23.2; 22.6–31.5 | 9.3 14.3; 6.6–12.1 |
|                            |                           | 34.4 19.5; 26.5–42.2 | 41.9 16.1; 35.4–48.4 | 36.3 19.4; 28.4–44.1 | 30.6 26.1; 20.0–41.2 |
|                            |                           | 53.5 22.7; 47.1–59.8 | 64.6 | 57.8 20.9; 52.0–63.7 | 47.1 29.9; 38.7–55.5 |

Abbreviation: COPD, chronic obstructive pulmonary disease; NON-AE, non-exacerbators; ACO, asthma-COPD overlap; AE, frequent exacerbators; mMRC, modified Medical Research Council; CAT, COPD Assessment Test; SGRQ-c, St George's Respiratory Questionnaire COPD; SD, standard deviation; 95% CI, 95% confidence interval

p-values with bold are significant

Table 2. mMRC, CAT) and SGRQ-c scores of COPD patients according to their COPD phenotypes
Patients with AE had significantly higher score in each item of CAT and each component of SGRQ-c compared to those with NON-AE (all p < 0.001) (Fig. 2 and Fig. 3). Patients with AE also had significantly higher score in CAT 3 (p = 0.004), CAT 4 (p = 0.008), CAT 5 (p = 0.013), CAT 6 (p = 0.003) and CAT 8 (p = 0.016); as well as symptoms (p < 0.001), activities (p < 0.001), and impacts (p = 0.005) components of SGRQ-c, when compared to ACO patients. Compared to NON-AE patients, ACO patients had significantly higher score in each item of CAT (p = < 0.001–0.040) except CAT 2; as well as symptoms and impact components of SGRQ-c (p < 0.001).

The total CAT and SGRQ-c scores of the only nine AE NON-CB patients were significantly higher than that of NON-AE (12.6 9.1 versus 5.5 4.7, p = 0.018; 47.6 18.5% versus 16.4 14.8 < 0.001), but not significantly different when compared to AE-CB or ACO.

**Discussion:**

The most frequent COPD phenotype in this unselected population in the rural setting of Malaysia was NON-AE, followed by the AE-CB, ACO and AE NON-CB. Patients with AE were significantly older and smoked more cigarettes, while patients with ACO were predominantly female. Regardless of the COPD phenotypes, biomass fuel exposure was a common risk factor of COPD among them. More than three-fifths of the patients were exposed to biomass fuel.

The HRQoL of patients with AE and ACO was markedly impaired compared to normal individuals. Meanwhile, the HRQoL of patients with NON-AE was reduced when measured by SGRQ-c but not by CAT. The worst HRQoL was reported in AE, with ACO coming next. The HRQoL of patients with AE was significantly worse than that of ACO and NON-AE while the HRQoL of ACO patients was significantly worse than the HRQoL of NON-AE patients. Similar pattern also observed in each item of CAT and each component of SGRQ-c, except the differences were not significant in cough, sputum, and sleep for AE versus ACO, as well as cough and daily activity limitation for ACO versus NON-AE. This lack of significance could be due to the smaller sample size of ACO, or the nature of bronchial asthma that predominantly diurnal in pattern and commonly associated with cough and sputum.

The distribution of COPD phenotypes in the present study was almost similar to western populations, (24–27) except the AE NON-CB was reported less than ACO.(28) So far, only two study reported AE CB was the commonest COPD phenotypes followed by NON-AE, AE NON-CB and ACO. The first study was conducted in the primary care centres of the Russia Federation,(29) while the second study involved selected COPD patients in the respiratory clinic of a tertiary hospital.(30) Our findings of patients with AE being older and smoked more cigarettes,(25, 27, 28, 31) as well as more female with the ACO phenotype are in agreement with other studies.(24, 26–28) The finding that the HRQoL of COPD patients was more impaired in the sequence of NON-AE, ACO and AE is consistent with the findings of previous studies.(24, 26–28, 32) Patients with AE were constantly highlighted as having the worst HRQoL,(24, 26–28, 31, 32) while those with NON-AE had the best HRQoL.(25, 29) Of patients with AE, Miravitlles et al,(28) Cosio et al,(31) Kania et al,(27) and Chai et al,(30) reported those with AE-CB had significantly worse HRQoL
compared to other COPD phenotypes (all p < 0.001); while Corlatenau et al reported the worst HRQoL in patients with AE NON-CB.(32) CAT was uniformly used to assess HRQoL in these studies, with the latter two studies also added on SGRQ-c. Only this study and that by Miravitlles et al,(28) show patients with ACO had significantly worse HRQoL than those with NON-AE.

Exacerbation is the prognostic hallmark of COPD. Frequent exacerbation is associated with poor HRQoL, (33) decline in lung function,(34) relapse of exacerbations,(33) recurrent hospitalisations,(35) and increased mortality.(36) Seemungal et al and Mackay et al, respectively reported COPD patients with ≥ three exacerbations (SGRQ-c, p < 0.001) and ≥ two exacerbations (CAT, p = 0.025) per year had significantly worse HRQoL.(33, 37) Cheng et al also reported COPD frequent exacerbators had significantly worse HRQoL (mMRC, p < 0.001; CAT, p < 0.001) compared to those without.(38) Therefore, this explained the significantly worse HRQoL among our patients with AE. Despite similar exacerbations frequency, our patients with ACO had significantly worse HRQoL than those with NON-AE which highlights that COPD subtypes could also affect the patients’ HRQoL. Miravitlles et al and Hardin et al, respectively reported COPD patients with BA had significantly worse HRQoL than those without [(mMRC, p = 0.008; SGRQ-c, p < 0.001), and (SGRQ-c, p = 0.008), respectively. (39, 40) Such a finding is not surprising in view of presence of two different inflammatory processes in ACO.

The findings of our study support the recommendation of GesEPOC to phenotype every COPD patients based on their exacerbation frequency and COPD subtypes.(15) Besides, this study also highlights that exacerbations frequency supersedes COPD subtypes in determining the patients’ HRQoL. Therefore, clinicians should manage COPD patients with frequent exacerbations more aggressively, considering pharmacotherapies such as long-acting muscarinic antagonist (LAMA), LAMA and long-acting β2-agonist in combination, inhaled corticosteroids (ICS), roflumilast, macrolide, or N-acetylcysteine, as clinically indicated.(1) COPD treatment should also be personalised according to COPD subtypes, such as ICS for ACO, roflumilast for CB, and medical or surgical lung volume reduction for emphysema, as clinically indicated.(1)

The present study is among the few in Asia that compare the HRQoL of COPD patients based on different clinical phenotypes. All the patients in this study were from the rural area. Their characteristics were very different from previous studies, such as having a high incidence of significant exposure to biomass fuel, required good physical fitness for agriculture activities, and had limited access to more expensive or newer COPD medications. Besides, we evaluated the HRQoL by using different HRQoL assessment tools and compared each of the sub item or component. By doing so we aimed to assess the patients’ HRQoL in more dimensions and to minimise biases.

There were several limitations in this study. Firstly, the number of AE NON-CB patients was disproportionately small and therefore we were unable to analysed it independently. We added AE NON-CB to AE-CB, and analysed in the line of AE for HRQoL analysis. Secondly, the direct comparison of CB versus emphysema subtypes was not possible because of the first limitation. Thirdly, the spirometry utilised FVC₆ instead of force vital capacity, potentially excluding a proportion of patients with mild
COPD. Fourthly, ACO in this study was defined based on history of BA and very reversible spirometry. Blood eosinophil count was not routinely performed in the rural areas. Lastly, the exacerbation frequency was subjected to the recall error of the patients. We tried to minimize this error by confirmation from patients’ medical records and family members.

Conclusions:

The present study concludes that HRQoL of patients with different COPD phenotypes is not the same. Patients with AE had the worst HRQoL, followed by those with ACO and NON-CB. The findings of this study support the recommendation of GesEPOC to phenotype and manage COPD patients based on their exacerbation frequency and COPD subtypes. COPD management should be personalised and more aggressive in frequent exacerbators to improve their poor HRQoL.

Abbreviations:

COPD, chronic obstructive pulmonary disease; HRQoL, health-related quality of life; PB-FEV1, post-bronchodilator forced expiratory volume in 1 second; PB-FVC₆, post-bronchodilator forced vital capacity in 6 seconds; mMRC, modified Medical Research Council; CAT, COPD Assessment Test; SGRQ-c, St Georges Respiratory Questionnaire for COPD; PB-FEV₁ %, PB-FEV₁ in % of predicted; GesEPOC, Spanish COPD guideline; NON-AE, non-exacerbator phenotype; AE, exacerbator phenotype; AE CB, exacerbator phenotype with chronic bronchitis; AE NON-CB, exacerbator phenotype with emphysema; BA, bronchial asthma; ACO, asthma-COPD overlap phenotype; SD, standard deviation; 95% CI, 95% confidence interval; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroids.

Declarations

Ethics Approval and Informed Consent:

The ethics approval for this study was obtained from the Medical Research and Ethic Committee of National Medical Research Registry Malaysia (NMRR-17-2549-38621) and the respective hospitals. Written informed consent was obtained from every patient.

Consent for publication:

Not applicable.

Availability of Data and Materials:

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

Competing 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:**

1. All the authors including Chee-Shee Chai, Sumastika Bt Mos, Diana-Leh-Ching Ng, Greta-Miranda-Kim-Choo Goh, Anselm-Ting Su, Muhammad Amin B Ibrahim, Aisya Natasya Bt Musa, Seng-Beng Tan, Yong-Kek Pang, and Chong-Kin Liam had contributed substantially to this study, which includes:

2. Substantial contributions to conception and design, data acquisition, or data analysis and interpretation;

3. Drafting the article or critically revising it for important intellectual content;

4. Final approval of the version to be published; and

5. Agreement 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
Figure 2

Score of CAT items according to the COPD phenotypes

Figure 3

Score of SGRQ-c total and components according to COPD phenotypes.