# VALIDATION OF SGRQ-CM, RISK FACTORS OF LUNG FUNCTIONS DETERIORATION AND ECONOMIC EVALUATION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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**by**

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| ATS | American Thoracic Society |
| ABC | Activity Based Costing |
| AECOPD | Acute exacerbation of COPD |
| BMI | Body mass index |
| COPD | Chronic obstructive pulmonary disease |
| CAT | COPD assessment test |
| CRQ | Chronic Respiratory Questionnaire |
| CCI | Charlson comorbidity Index |
| CPI | Consumer Price Index |
| CRP | C-reactive protein |
| CT scan | Computed tomography scan |
| Cronbach's α | Cronbach's alpha coefficient |
| CFA | Confirmatory factor analysis |
| DLCO | Diffusion capacity of carbon monoxide |
| EQ-5D-5L | European Quality of life 5-Dimension 5-Level questionnaire |
| EQ-5D-5L UI | European Quality of life 5-Dimension 5-Level questionnaire Utility index score |
| EQ-VAS | European Quality of life 5-Dimension 5-Level questionnaire Visual analogue score |
| ED | Emergency department |
| EFA | Explanatory factor analysis |
| FEV1 | Forced expiratory volume in one second |
| FVC | Forced vita capacity |
| FEV1 % | FEV1 % predicted of the normal value |
| FDA | Food and Drug Administration Authority |
| FC | Friction cost approach |
| GOLD | Global Initiative for Chronic Obstructive Lung Disease |
| HQOL | Health related quality of life |
| HC | Human capital approach |
| IL | Interleukin |

| | |
|---|---|
| ICS | Inhaled corticosteroids |
| ICD-9 | International Classification of Diseases 9th version |
| ICD-10 | International Classification of Diseases 10th version |
| ICC | Intraclass correlation coefficients |
| LTOT | Long term Oxygen therapy |
| LABA | Long-acting beta2-agonists |
| LAMA | Long-acting antimuscarinic agents |
| %LAA=-950 | Attenuation lower than -950 Hounsfield Units. |
| mMRC | Modified Medical Research Council dyspnea scale |
| MCID | Minimum clinically important difference |
| MMP-9 | Serum matrix metalloproteinase-9 |
| NMRR | National Medical Research Register Malaysia |
| PR | Pulmonary rehabilitation; |
| Pa CO2 | Arterial partial pressure of CO2 |
| RR | Relative risk |
| SGRQ | St. George's Respiratory Questionnaire |
| SGRQ-C | St George's respiratory COPD specific questionnaire |
| SGRQ-CM | Malaysian version of St George's Respiratory COPD specific questionnaire |
| 6MWD | Six minute walking distance test |
| SABA | Short-acting beta2-agonists |
| SAMA | Short-acting antimuscarinic agents |
| TIMP-1 | Metalloproteinase-1 |
| TNF-α | Tumor necrosis factor α |
| USD | United State dollars |
| US$ | United State dollars |
| WPAI-COPD | Work Productivity and Activity Impairment Questionnaire: COPD specific V2.0 |
| WHO | World health organization |
| WBCs | White blood cells |

**VALIDASI SGRQ-CM, FAKTOR RISIKO KEMEROSOTAN FUNGSI PARU-PARU DAN PENILAIAN EKONOMI DALAM PESAKIT PULMONARI OBSTRUKSI KRONIK**

## ABSTRAK

Status kesihatan dan penurunan $FEV_1$ adalah dua faktor yang penting bagi 'GOLD' (Inisiatif Global bagi penyakit obstruktif pulmonari kronik) sistem pentaksiran multi dimensi. Pendekatan ini menggunakan alat pentaksiran status kesihatan berdasarkan simptom, '$FEV_1$' dan risiko berdasarkan frekuensi eksaserbasi untuk mengklasifikasi pesakit menurut kepada keterukan penyakit kepada empat kumpulan 'GOLD' A sehingga D dan untuk mencadangkan terapi famako yang optimum. Keterukan status kesihatan (peningkatan dalam beban simptom), penurunan dalam $FEV_1$ atau peningkatan dalam frekuensi eksaserbasi boleh mengakibatkan kemaraan penyakit dari kumpulan yang rendah kepada kumpulan yang tinggi. 'COPD' juga dikaitkan dengan beban ekonomi yang banyak terhadap individu dan masyarakat. Maka, objektif bagi kajian ini adalah untuk mentaksir beban ekonomi akibat 'COPD', untuk mengesahkan soal selidik spesifik bagi 'St George's Respiratory COPD' versi Malaysia sebagai alat pentaksiran status kesihatan dan mengenalpasti faktor risiko menurunan '$FEV_1$' dalam pesakit 'COPD'. Ini merupakan kajian prospektif cohort secara longitudinal melibatkan 367 pesakit COPD dari Hospital Besar Pulau Pinang. Pengesahan, kebolehpercayaan, maklum balas dan perbezaan minimum kepentingan klinikal (MCID) soal selidik SGRQ-C versi Malaysia telah dinilai unutk diguna pakai dalam populasi Malaysia. Regresi 'Cox' secara univariat dan multivariat berserta varians yang teguh telah dijalankan untuk menganggar risiko relative

(RR) bagi faktor yang berlainan terhadap penurunan '$FEV_1$' selepas rawatan lanjutan selama setahun. Penentuan kos berdasarkan aktiviti, pendekatan atas bawah telah digunakan untuk mengira kos lansung, manakala kos tidak lansung pesakit telah dinilai menggunakan soal selidik terhadap produktiviti kerja dan gangguan aktiviti. Koefisi 'chronbach alpha' dan koefisi korelasi antara kelas nagi 'SGRQ-CM telah dilaporkan masing-masing sebagai 0.87, dan 0.88. Korelasi 'SGRQ-CM' dengan 'CAT', 'EQ-5D-5L', skala dispnea 'mMRC' dan jangkaan peratus '$FEV_1$' telah dilaporkan masing-masing sebagai 0.86, -0.82, 0.72 dan -0.42. MCID telah dilaporkan sebagai 5.07. Sepanjang durasi kajian ini, purata penurunan $FEV_1$ telah dilihat sebagai 27.35 (11.34) ml, manakala 109(30.27%) pesakit menunjukan purata penurunan '$FEV_1$' sebanyak ≥60ml. Analisis regrasi menunjukan RR tabiat merokok terkini ialah = 2.38 (1.78-3.07), $p<0.001$); RR bagi GOLD peringkat III & IV = 1.43 (1.27-1.97), $p<0.001$); RR bagi skor mMRC 3 ke 4 = 2.03 (1.74-2.70), $p<0.01$); RR bagi perbezaan sebanyak ≥10 skor 'SGRQ-C' = 2.01 (1.58-2.73), $p<0.01$); RR bagi 6MWD <350m= 2.29 (1.87-3.34), $p<0.01$); RR bagi eksaserbasi ≥3 dalam tahun kajian = 2.28 (1.58-2.42, $p<0.001$); RR bagi indek komorbiditi 'Charlson'(CCI) ≥ 3 RR = 3.18 (2.23-3.76), $p<0.01$) dan RR bagi emfisema = 1.31 (1.15-1.79), $p<0.01$) merupakan faktor risiko yang siknifikan bagi kemerosotan fungsi paru-paru secara pantas (penurunan '$FEV_1$' ≥60ml). Purata kos lansung dan tidak lansung tahunan bagi pengurusan 'COPD' setiap pesakit menujukan bukti pengesahan, kebolehpercayaan, maklum balas yang kuat. Di antara faktor yang berlainan, skor CCI ≥3, penurunan status kesihatan secara tiba-tiba, frekuensi eksaserbasi ≥ 3, jumlah hari kemasukan hospital ≥ 8 dan emfisema telah dilaporkan sebagai faktor risiko bagi penurunan fungsi paru-paru secara pantas. 'COPD' juga telah dikaitkan dengan beban ekonomi terhadap pesakit dan masyarakat yang penting.

# VALIDATION OF SGRQ-CM, RISK FACTORS OF LUNG FUNCTIONS DETERIORATION AND ECONOMIC EVALUATION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

## ABSTRACT

Health status and $FEV_1$ decline are two important factors of the GOLD (Global initiative for chronic Obstructive Lung Disease) multidimensional assessment system. This approach uses symptoms based on health status assessment tools, degree of airflow limitation ($FEV_1$) and risk based on exacerbation frequency to classify patients according to disease severity into four groups GOLD A to D and propose optimum pharmacotherapy. Worsening of health status (increase in symptoms load), decline in $FEV_1$ or increase in exacerbation frequency can result in progression of disease from lower to higher group. COPD is also associated with considerable economic burden on the individual and society. Thus, objectives of the current study were to assess the economic burden of COPD, validate the Malaysian version of St George's Respiratory COPD specific questionnaire (SGRQ-CM) as health status assessment tool and find the risk factors of $FEV_1$ decline in COPD patients. This was a longitudinal prospective cohort including 367 COPD patients from Penang Hospital. Validity, reliability, responsiveness and MCID (minimum clinical important difference) of the of the Malaysian version of SGRQ-C was assessed to be used in population of Malaysia. Univariate and multivariate Cox regression with robust variance were performed to estimate relative risk (RR) for different factors on decline in $FEV_1$ after one year of follow up. Activity-Based Costing, bottom-up approach was used to calculate direct cost, while, indirect costs of the patients were assessed using the Work

Productivity and Activity Impairment Questionnaire. The Cronbach alpha coefficient and intraclass correlation coefficients (ICC) for SGRQ-CM were reported as 0.87, and 0.88 respectively. Correlation of SGRQ-CM with CAT, EQ-5D-5L, mMRC dyspnea scales and $FEV_1$% predicted were reported as 0.86, -0.82, 0.72 and -0.42 respectively. The MCID was reported as 5.07. During the study period mean decline in $FEV_1$ was observed as 27.35 (11.34) ml, while 109 (30.27%) patients showed mean decline of ≥60ml in $FEV_1$. The regression analysis showed that current smoking relative risk (RR) = 2.38 (1.78-3.07), p<0.001); GOLD Stage III& IV RR = 1.43 (1.27-1.97), p<0.001); mMRC score 3 to 4 RR = 2.03 (1.74-2.70), p<0.01); SGRQ-C score≥10 points difference RR = 2.01 (1.58-2.73), p<0.01); 6MWD <350m RR = 2.29 (1.87-3.34), p<0.01); ≥3 exacerbation in study year RR = 2.28 (1.58-2.42, p<0.001); Charlson comorbidity index (CCI) ≥ 3 RR = 3.18 (2.23-3.76), p<0.01) and emphysema RR = 1.31 (1.15-1.79), p<0.01) were significant risk factors for the rapid deterioration of lung function ($FEV_1$ decline ≥60ml). Mean annual per-patient direct cost and indirect cost for the management of COPD was calculated as US$ 506.92 and US$ 1699.76 respectively. The Malaysian version of SGRQ-C showed strong evidence of validity, reliability and responsiveness. Among different factors CCI score ≥3, abrupt decline in health status, exacerbation frequency ≥ 3, hospital admission days≥ 8 and emphysema were reported as risk factors for rapid deterioration of lung function. COPD was also associated with substantial economic burden on patients and society.

# CHAPTER 1

# INTRODUCTION

## 1.1 Epidemiology of Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disorder characterized by persistent and progressive airflow obstruction, which significantly affects clinical, epidemiological and socioeconomic status of patients. Globally the prevalence of COPD range from 3.5% to 19.1% (Buist et al., 2007). In Europe and USA, the prevalence of COPD range from 3.4% to 13.4% (Blanco et al., 2018; Buist et al., 2007). Whereas, in Asia, its prevalence range from 3.5% to 19.1%, among which one-fifth are suffering from severe or very severe COPD (GOLD, 2019). COPD prevalence is increasing in Asia due to urbanization, industrial pollution, tanneries and biomass fuel burning inside homes (Buist et al., 2007). World health organization (WHO) estimated that COPD prevalence will increase 3 folds in Asia as compared to the rest of world until 2030 (WHO, 2018). Increasing prevalence in Asia is affecting the whole word, and it is projected that COPD will become the second largest diagnosis after diabetes worldwide by 2030 (Buist et al., 2007). In Malaysia, approximately 448,000 cases were reported in 2010 with an estimated burden of RM 2.8 billion (Hassan et al., 2014). International Tobacco Control Malaysia report in 2012, reported a drastic increase in smoking in adult males (46.4%) and slight increase in females (1.6%), which may result in an increase in the prevalence of COPD in Malaysia ("ITC Malaysia National Report," 2012; Shahab et al., 2006). COPD is the 4th leading cause of hospital admissions in Malaysia ("ITC Malaysia National Report," 2012), which causes substantial burden on the already stretched resources health care system of Malaysia.

WHO reported COPD as the third leading cause of death, which is responsible for 3 million deaths every year worldwide (WHO, 2018). In year 2004, COPD was responsible for 5.1% of the total deaths that occurred in that year, which increased to 6% by the end of 2012, and is expected to rise further to 8.6% by 2030 (Molinari et al., 2016). Approximately 90% of deaths related to COPD occur in Asia and Africa (May et al., 2015). The death rate due to COPD is 3.2 times higher in Asia than USA and Europe (May et al., 2015). While smoking is the most important risk factor for initiation of COPD, other risk factors include pollution, environmental conditions, occupational exposure, biomass fuel burning, atopy, alpha-1 antitrypsin deficiency, antioxidant deficiency, respiratory infections, asthma, development abnormalities, biomass exposure, occupational hazards and noxious stimuli (GOLD, 2019). Global burden of COPD is increasing due to continuous exposure to risk factors (GOLD, 2019). The current understanding of risk factors for COPD is in many respects still incomplete (GOLD, 2019).

## 1.2 Exacerbation of COPD

COPD exacerbation is characterized by clinical instability and worsening of COPD symptoms. Exacerbation can be life-threatening for certain patients and requires hospitalization or emergency department treatment (Polatli et al., 2012). In 2013 hospital admissions due to COPD accounted for 13% of all hospital admissions of that year, and it gained a massive share in the healthcare budget of developed countries (de Oca et al., 2016). COPD patients experienced 5 times more hospital admissions and require 3 times more healthcare specialist consultation than non-COPD patients (Rothnie et al., 2016). It is projected that within 5 years, COPD exacerbation will be the leading cause of hospitalization worldwide, surpassing Ischemic heart disease, which is currently the

leading cause of hospitalization (Han et al., 2017; Khakban et al., 2017). It causes substantial social and economic burden on patients and healthcare systems (Rehman et al., 2020; ur Rehman et al., 2019).

### 1.3 Diagnosis of COPD

Spirometry test is a GOLD (Global initiative for chronic obstructive lung disease) recommended COPD diagnostic test and is one of the most reliable and reproducible measurements of airflow obstruction (GOLD, 2019). In patients showing persistent episodes of dyspnea, wheezing or chest tightness, chronic cough or sputum production (for ≥3 months in two consecutive years), recurrent lower respiratory tract infection, and/or a history of exposure to risk factors the presence of COPD is confirmed via spirometry (GOLD, 2019). Spirometry test quantified as post-bronchodilator forced expiratory volume in 1 second ($FEV_1$)/ forced vita capacity (FVC) < 0.70 confirms the presence of COPD. $FEV_1$/FVC is evaluated by comparison with reference values based on age, height, sex, and race and is presented as $FEV_1$ % predicted of the normal value ($FEV_1$ %) (GOLD, 2019). Due to easy to use and reproducibility, current diagnosis system rely on it as an indicator of disease progression and categorize COPD patients on the basis of airflow limitation (GOLD, 2019). On the basis of severity of airflow limitation the COPD patients are categorized into 4 categories, mild or Grade I COPD with $FEV_1 \geq 80\%$ predicted, moderate or grade II with $FEV_1$ 50% to 80% predicted, severe or grade III at $FEV_1$ 30% to 50% predicted and very severe or grade IV with $FEV_1 < 30\%$ predicted (GOLD, 2019).

## 1.4 Assessment of COPD

Novel multidimensional approach recommended by GOLD 2011 and onward updates uses symptomatic assessment in addition to spirometry to assess and categorize COPD patients. The novel multidimensional approach recommend the assessment of COPD based on the severity of symptoms, degree of airflow limitation and risk for future events (measured as rate of $FEV_1$ decline or exacerbation frequency) to categories COPD patients in four groups (A, B, C and D) and propose a particular pharmacotherapy (GOLD, 2019). Symptoms severity is assessed with the help of health status measures (mMRC, CAT or SGRQ-C), degree of airflow limitation is assessed as $FEV_1$ % value and risk to progression of disease is assessed as exacerbation frequency or $FEV_1$ % decline, whatever results in a higher risk. GOLD Multidimensional approach to categorize COPD patients is presented in Table 1.1.

Table 1.1 Multidimensional approach to categorize COPD patients into different severity groups

| GOLD Category | Characteristic | Spirometric classification | Exacerbation frequency | Health Status measure |
|---|---|---|---|---|
| GOLD A | Low risk, less symptoms | GOLD I -II | ≤2/year | Lower score |
| GOLD B | Low risk, more symptoms | GOLD II -III | ≤2/year | Higher score |
| GOLD C | High risk, less symptoms | GOLD II-III | >2/year | Lower score |
| GOLD D | High risk, more symptoms | GOLD III-IV | >2/year | Higher score |

*Grade I COPD with $FEV_1$≥80% predicted, grade II with $FEV_1$ 50% to 80% predicted, grade III at $FEV_1$ 30% to 50% predicted and grade IV with $FEV_1$<30% predicted; higher Score for SGRQ≥25; higher score for CAT ≥10; higher score for mMRC≥2.*

### 1.4.1 Assessment of Symptoms Burden

Health status questionnaires are used to assess the symptoms burden and health status in COPD patients (Jones et al., 1994).

#### 1.4.1(a) Modifies medical research council dyspnea scale

Initially in 2011 mMRC was added as health status measure to assess the symptoms load and their impact on quality of life of COPD patients. The mMRC is a self-administered FDA approved health status measure. It has been used for years to assess the level of breathlessness and its impact on daily activities on a scale from 0 to 4 (Grade 0: not troubled by breathlessness except on strenuous exercise, Grade 1: Short of breath when hurrying or walking up a slight hill, Grade 2: walks slower than contemporaries on level ground because of breathlessness, Grade 3: Stops for breath after walking about 100 meters (109 yards) or after a few minutes on level ground, Grade 4: too breathless to leave the house or breathless when dressing or undressing) (Mahler et al, 1986). It was considered adequate to assess symptoms as dyspnea is considered as a key symptom of COPD.

#### 1.4.1(b) COPD assessment test

However, COPD affects patients beyond just dyspnea. A comprehensive and disease specific questionnaire can assess the true impact of disease on health status of COPD patient. For this reason, later in 2013 COPD assessment test (CAT) and in 2018 St. George's Respiratory COPD specific Questionnaire (SGRQ-C) were added in clinical

assessment to assess symptom burden of COPD patients and categorize according to severity of disease and recommend specific therapies. CAT is an FDA approved health status questionnaire used for assessment of COPD patients. CAT is easy to understand and consist of 8 items related to symptoms and activities. Each item has scores 0 to 5 from best to worst with a maximum total score of 40 (Jones et al., 2009).

### 1.4.1(c) The St. George's Respiratory COPD specific Questionnaire

CAT is a short form of SGRQ-C and can only measure respiratory disability and few activities among patients with COPD (Karloh et al., 2016). CAT can measure the symptomatic impact of COPD but can't effectively categorize patients according to severity of symptoms. SGRQ-C gives brief detail about symptoms severity, physiological functioning, functional impairment and their impact on health status of patient. The SGRQ-C comprise of 40 items and is divided into 3 subscales; Symptoms (problems caused by specific respiratory symptoms); Activity (restriction of activity by dyspnea); and Impacts (impact on everyday life caused by the disease). Each item has a predetermined weight, which is combined to calculate the subscale score and total score. Scores are expressed as percentages of the maximally possible sum of weights. Total score and each subscale score range from 0 to 100, with 0 best possible and 100 worst possible score (Meguro et al., 2007). SGRQ-C is the most widely used questionnaire in scientific research and clinical trial. It has good reliability and sensitivity to clinical changes in COPD patients in many countries (Weldam et al., 2013). Based on the results of different clinical trials a threshold of ≥25 points is used to categorize patients according to disease severity (GOLD, 2019).

### 1.4.2 Airflow Limitation

Airflow limitation is assessed by $FEV_1$% value. As discussed above before 2011 it was the sole measure to categorize COPD patients. It is the most widely used severity measure in clinical studies (GOLD, 2019). Its already been discussed in detail in diagnosis part.

### 1.4.3 Future Risk

The future risk of exacerbation is assessed in terms of exacerbation frequency. Exacerbation increases the lung function deterioration and mortality risk. History of exacerbation is the best predictor of future exacerbations. Patients experiencing ≥2 exacerbations in last year are considered at higher risk. In addition degree of airflow limitation ($FEV_1$%) is also associated with increased exacerbation frequency and can be used to predict exacerbation (Young et al., 2007). The risk of exacerbation is significantly higher in GOLD III and GOLD IV COPD patients.

## 1.5 Management of COPD

Availability of resources and physicians' knowledge and experience play a vital role in managing and treating COPD. The primary objectives of COPD management are to control symptoms, reduce risk (prevent disease progression and exacerbation), restoring the daily activities of the patients and minimizing the impact of disease on patients' quality of life. (Adeloye et al., 2015). No available medication for COPD can modify the long-term decline in lung function. Available therapy can only slow down the progression of disease (ur Rehman et al., 2019). A combination of pharmacological and non-

pharmacological management has been shown to be useful for the better control of symptoms, reduce exacerbation frequency and improving routine activities to live a healthy life (ur Rehman et al., 2019). Identification and reduction of exposure to risk factors is key strategy in management of COPD patients. Ongoing monitoring should include continuous evaluation of exposure to risk factors and monitoring of disease progression. Smoking cessation and reduces exposure to occupational hazards can increase the efficacy of pharmacological management.

### 1.5.1 Pharmacological management of COPD

Pharmacological therapy for COPD is used to improve health status, control symptoms and diminish the severity and frequency of exacerbations. In patients with mild to moderate COPD [GOLD class A and B], GOLD guideline recommends prescription of short-acting and long acting bronchodilators which include short-acting beta2-agonists (SABA), short-acting antimuscarinic agents (SAMA), long-acting beta2-agonists (LABA) and long-acting antimuscarinic agents (LAMA) alone or in combination, depending upon the condition and severity of COPD (GOLD, 2019). Preferred pharmacological treatment is demonstrated in Figure 1.1.

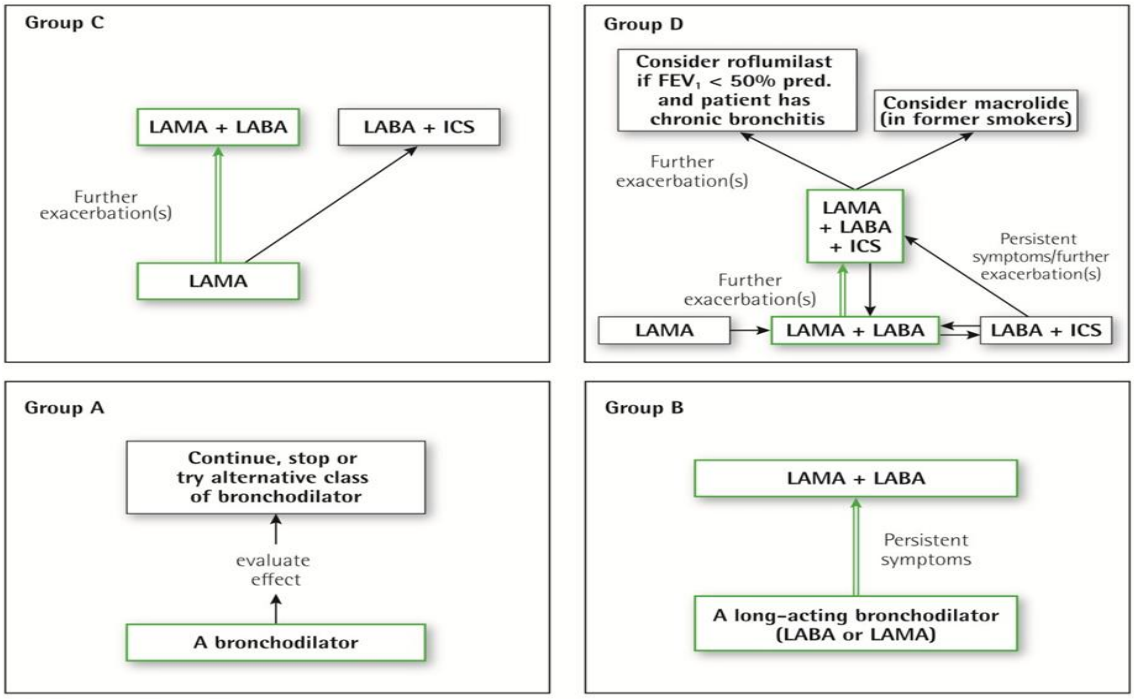


Figure 1.1 Pharmacological treatment algorithm by GOLD grade adopted from GOLD report (2019)

*Taken with permission from GOLD report 2019; Highlighted arrow indicates preferred treatment; GOLD, Global initiative for chronic Obstructive Lung Disease; mMRC, modified Medical Research Council; GOLD A, low risk, less symptoms; GOLD B, low risk, more symptoms; GOLD C high risk, less symptoms; GOLD D, high risk, more symptoms; ICS, Inhaled corticosteroids; LABA, long-acting beta2-agonists; LAMA, long-acting antimuscarinic agents; SABA, short-acting beta2-agonists; SAMA, short-acting antimuscarinic agents.*

### 1.5.1(a) Bronchodilators

Bronchodilators are mostly used for the management of COPD and have showed no effect on mortality. Formoterol and salmeterol are twice-daily LABAs and Indacaterol, Oladaterol and vilanterol are once daily LABAs improve dyspnea. SAMAs, such as ipratropium and oxitropium and LAMAs, such as aclidinium, glycopyrronium bromide, Tiotropium and umeclidinium inhibit bronchoconstriction of airway smooth muscles (Melani, 2015). Wider use of antimuscarinic agents in a wide range of doses and clinical settings has shown them to be very safe and they cause bronchodilation with minimum

side effects (Tashkin, 2010). Among methylxanthines, Theophylline is widely used oral bronchodilator in low-income countries because of its low cost and easy accessibility. Addition of Theophylline to LABA significantly improves the lung function and dyspnea (ZuWallack et al., 2001). It may be prescribed as an alternative in the absence of bronchodilators. Major problem related to methylxanthines is its safety in COPD patients. Most frequently noticed adverse effects related to methylxanthines treatment include insomnia, nausea, headaches, fatal atrial and ventricular arrhythmias, heartburn and convulsions (Ram et al., 2002). Bronchodilators increase $FEV_1$ value, improve lung function and exercise tolerance and reduce hyperinflation of lungs (Hay et al., 1992). In addition to better efficacy, these agents require low dosing frequency which increases patient compliance and adherence to therapy thus improving clinical effects.

For GOLD class C and D patients with a continued high eosinophil count or frequent exacerbations even after LABA/LAMA combination, inhaled corticosteroids (ICS) are added to the therapy (Busa et al., 2018). Other key treatment options include macrolides and PDE4 inhibitors. Treatment of COPD patients with ICS alone has shown no effect on lung function and mortality rate (Yang et al., 2012). Addition of ICS to LABA enhances the efficiency of LABA and ICS/LABA combination therapy in severe COPD patients proved more effective that either component alone in improving dyspnea and reducing the exacerbation relapse (Vestbo et al., 2016). ICS/LABA combination may results in approximately 8.4% reduction in frequency of moderate-to-severe exacerbations and lower risk of the death outcome (36.4% vs 37.3%) as compared to LABAs alone (Vestbo et al., 2016).

Adding a LAMA to LABA/ICS combination improves lung function and control of symptoms in patients who are unresponsive to dual combination therapy and who are at elevated risk of frequent exacerbations (Papi et al., 2018). The results of different (randomised controlled trials) RCTs showed that triple therapy was associated with better control of symptoms and lower risk of moderate or severe exacerbations than dual or mono therapy, with a similar adverse effect profile to that of dual and mono therapy in severe COPD patients (Lipson et al., 2018).

### 1.5.1(b) Phosphodiesterase-4 [PDE4] inhibitors

Roflumilast is a widely used Phosphodiesterase-4 [PDE4] inhibitor. Roflumilast may act as non-selective phosphodiesterase inhibitor and has no direct bronchodilator activity. An RCT demonstrated that addition of Roflumilast to LABA or LABA/ICS combination in severe to very severe COPD patients, with a history of exacerbations improves the responsiveness of therapy, improve lung function and reduces exacerbation (Martinez et al., 2015).

### 1.5.1(c) Antibiotics

Antibiotics i.e. azithromycin or erythromycin are mostly prescribed during exacerbation (Woodhead et al., 2011) The risk of exacerbations reduces in antibiotic treated patients as compared to usual care. A systematic review of placebo-controlled studies have demonstrated that antibiotics diminish the sputum purulence by 44%, treatment failure by 53% and risk of short-term mortality by 77% (Nair et al., 2017). A recent study demonstrated that avoiding the use of antibiotics in COPD patients with

exacerbations requiring mechanical ventilation was associated with high risk of nosocomial pneumonia and elevated mortality (Mathioudakis et al., 2017). Drugs used in the treatment of COPD and their duration of action are demonstrated in Table 1.2.

Table 1.2 Drugs recommended for the management of COPD

| Class | Drugs | Duration of Action (Hours) | Recommendations |
|---|---|---|---|
| $Beta_2$-Agonists | SABA | | Central to symptom management<br>Given on regular basis<br>Improve $FEV_1$<br>Long-acting agents are preferred over short-acting agents.<br>Inhaled bronchodilators are preferred over oral ones |
| | Fenoterol | 4-6 | |
| | Levalbuterol | 6-8 | |
| | Salbutamol | 4-6 | |
| | Terbutaline | 4-6 | |
| | LABA | | |
| | Arformoterol | 12 | |
| | Formoterol | 12 | |
| | Indacaterol | 24 | |
| | Oladaterol | 24 | |
| | Salmeterol | 12 | |
| | Vilanterol | 24 | |
| Anticholinergics | SAMA | | Improve effectiveness of PR<br>Added to LABA to synergize effect<br>Can be used as first line therapy<br>Equal effective as LABA |
| | Ipratropium bromide | 6-8 | |
| | Oxitropium bromide | 7-9 | |
| | Aclidinium bromide | 12 | |
| | LAMA | | |
| | Glycopyrronium bromide | 12-24 | |
| | Tiotropium | 24 | |
| | Umeclidinum | 24 | |
| SABA/SAMA combination | Fenoterol/ Ipratropium | 6-8 | More efficient than either agent alone<br>Better improvement in lung function, dyspnea<br>Reduce exacerbation frequency better than monotherapy or LABA/ICS combination<br>Decrease hospitalization |
| | Salbutamol/Ipratropium | 6-8 | |
| LABA/LAMA combination | Formoterol/Aclidinium | 12 | |
| | Formoterol/Glycopyronium | 12 | |
| | Indacterol/ Glycopyronium | 12-24 | |
| | Vilanterol/Umeclidinium | 24 | |
| | Formoterol/Glycopyrrolate | 12 | |
| | Olodaterol/Tiotropium | 24 | |
| Methylxanthines | Aminophyline | Upto 24 | Synergize the effect of bronchodilators |
| | Theophyline | Upto 24 | |

| | | | |
|---|---|---|---|
| LABA/ICS combination | Formoterol/Beclomethasone | | Preferred in patients with history of exacerbation<br>Better improvement in symptoms<br>Long term monotherapy is not recommended<br>Risk of Pneumonia |
| | Formoterol/Budesonide | | |
| | Formoterol/Mometasone | | |
| | Salmeterol/Fluticasone | | |
| | Vilanterol/Fluticasone furoate | | |
| Phosphodiestrase-4 inhibitors | Roflumilast | | Can synergize the effect of ICS/LABA combination therapy<br>Reduce exacerbation |

*ICS, Inhaled corticosteroids; LABA, long-acting beta2-agonists; LAMA, long-acting antimuscarinic agents; PR, pulmonary rehabilitation; SABA, short-acting beta2-agonists; SAMA, short-acting antimuscarinic agents.*

### 1.5.2 Non-pharmacological management of COPD

Nevertheless, goals to improve dyspnea, exercise tolerance and daily activities may not be able to achieve with pharmacological therapy alone without support from non-pharmacological management, which includes smoking cessation, pulmonary rehabilitation, immunization, oxygen therapy and surgical reduction of lung size (Akwe et al., 2016). Exercise to enhance lung capacity can improve the condition of COPD patients. Pulmonary rehabilitation and oxygen therapy are other non-pharmacological methods of managing the disease. Lung volume reduction surgery is recommended for patients with heterogeneous upper zone emphysema, and reduced exercise tolerance, which have been shown to be better than medical treatment with a substantial reduction of mortality in patients (GOLD, 2019; ur Rehman et al., 2019).

### 1.5.2(a) Risk factors exposure cessation

Proper management of the disease through attaining healthy lifestyle and avoiding risk factors can play a key role in controlling and slowing down the progression of the disease. Studies show that there are certain unmodifiable risk factors that might affect a person's susceptibility to the initiation and development of COPD, i.e. genetic susceptibility and gender (Han et al., 2007). But most of the risk factors for initiation of COPD are preventable and modifiable. The modifiable risk factors, including tobacco smoking, and occupational exposure.

Smoking is responsible for most of the cases of respiratory diseases especially COPD. Thus, smoking cessation is considered as the most important avoidable risk factor in the management of COPD. Smoking cessation plays a significant role in halting the decline of lung function, especially in acute and moderate COPD patients. Smoking cessation may reduce the destruction of lung function to half as compared to smokers thus decrease the development of COPD (Salvi et al., 2014). An RCT demonstrated significant improvement in lung functions and $FEV_1$ value in stage I and stage II COPD patients after one year of smoking cessation and subsequent rate of decline in FEV1 was half the rate of decline than in smokers. Smoking cessation, improved respiratory symptoms, i.e. chronic cough, sputum production, wheezing and dyspnea and reduces the risk of lower respiratory tract infections and frequent exacerbations (Wu & Sin, 2011).

### 1.5.2(b) Vaccination

COPD patients possess a high risk of respiratory illnesses such as pneumonia and influenza, which result in COPD exacerbations (Walters et al., 2017). GOLD report (2018,

2019) recommends influenza and pneumococcal vaccination for COPD patients. Results of a meta-analysis showed that polyvalent pneumococcal vaccination against community-acquired pneumonia and influenza vaccination against influenza-related acute respiratory illness (ARI) resulted in substantial reduction in likelihood of exacerbation of COPD and decreased hospitalization frequency due to pneumonia. Vaccination showed no effects on mortality rate and other symptoms of COPD (Latifi-Navid et al., 2018).

### 1.5.2(c) Pulmonary Rehabilitation

Pulmonary Rehabilitation (PR) therapy is considered as a key component in the management of severe COPD to improve lung function, exercise tolerance and health related quality of life (HQOL) of COPD patients. It includes a series of activities including patients' assessment, education, training, nutrition, psychological and behavioral support which aid in improving lung function of the patients and increase compliance towards therapy (Spruit et al., 2013). PR has no effect on physiologic destruction, but it improves significant burden of patients by reducing dyspnea, chronic cough, sputum production and improving exercise tolerance and lung capacity and reduce the harmful effects of comorbidities in patients (Spruit et al., 2015). A collaboration of the pulmonary rehabilitation program with pharmacotherapy significantly improves quality of life of patients. An RCT in Canada reported a 40 % reduction of outpatient and inpatient visits in patients undergoing pulmonary rehabilitation and self-management education program at the same time (Sahin et al., 2018). Whole-body vibration [WBV] is a recently adopted rehabilitation technique, which is novel developed technique of neuromuscular training to

improve muscle strength, balance and mobility in stage IV COPD patients (Júnior et al., 2015).

### 1.5.2(d) Supplementary Oxygen

Oxygen is the first treatment shown to enhance survival rate and maximize quality of life of people with COPD. A long term clinical trial showed that treatment of exacerbations of COPD patients with titrated oxygen, reduced the pulmonary hypertension and improved the breathing pattern, exercise tolerance, mental and emotional states and artery pressure (Yusen et al., 2018). During COPD exacerbations that require hospitalization, oxygen therapy is a core part of treatment and should be initiated immediately to decrease morbidity and mortality and provide symptom relief. Ambulatory oxygen is prescribed for patients who are on LTOT (long-term oxygen therapy) but need to use oxygen outside the home or patients having exercise arterial desaturation. The NICE guideline suggested the use of supplementary oxygen at an interval of 10- 20 minutes [short-burst oxygen therapy] in COPD patients suffering from dyspnea to overcome the shortness of breath. However, it should be discontinued if there is no sign of improvement in breathlessness. Despite the benefits of oxygen treatment, it may cause potential side effects in COPD patients, including a significant increase in the arterial partial pressure of $CO_2$ [Pa $CO_2$] > 20mmHg and rebound hypoxemia on termination of oxygen therapy or in response to hypercapnia (Yusen et al., 2018).

## 1.6 Economic Burden due to COPD

Cost spent for a long term treatment, the use of specialized resources in the management of COPD, duration of illness and indirect cost due to work loss is associated with substantial economic burden on the individual and society (Ding et al., 2017; ur Rehman et al., 2019).

### 1.6.1 Direct cost

In 2004 the estimated cost for management of COPD in the USA was reported as $37.2 billion, which raised to $42.6 billion in 2007 and $49.9 billion in 2010 (Guarascio et al., 2013). Whereas, in Europe the cost of management of COPD raised from €38.6 billion in 2003 to €48.4 billion in 2011 (Kim et al., 2013; Rehman et al., 2019). The major cost factor of the direct medical cost is hospitalisation due to exacerbation, other factors include medication, oxygen therapy and health specialist visits. In 2013 hospital admissions due to COPD accounted for 13% of all hospital admissions of that year, and it gained a massive share in the health budget of developed countries (de Oca et al., 2016). In 2012 COPD patients incurred approximately 14% higher cost than non-COPD patients (D'Souza et al., 2014). Direct cost of management of COPD varies from 35% to 75% of the total cost among different countries (Shah et al., 2019; ur Rehman et al., 2019).

### 1.6.2 Indirect cost

COPD also results in significant economic burden to the patient and society resulting from productivity losses due to compromised quality of life, early retirement and disability pension (Ding et al., 2017). COPD causes limitations to daily activities, social

behaviour and sleeping pattern. It limits the daily activities and movement by 3 times, and working inability by 5 times than healthy people (May et al., 2015; Thornton Snider et al., 2012). Among working age patients COPD is the 11th leading cause of work productivity loss and is expected to be 7th till 2030 (WHO, 2018). In USA and UK approximately 40% to 60% patients diagnosed with COPD were of working-age (Rai et al., 2017). Employs diagnosed with COPD show higher absenteeism rate and compromised work performance at working place as compared to those without COPD or employees with other chronic conditions i.e. asthma and cardiovascular diseases (daCosta DiBonaventura et al., 2012; Holden et al., 2011). The monthly per capita income of COPD patients was reported approximately 34.1% less than healthy workers due to absenteeism from the workplace (Thornton Snider et al., 2012). COPD patients missed an average of 150 days per year from work and an average of 1.47 years of work due to early retirement and one third of the family income was associated with the management of COPD (May et al., 2015). Work productivity loss and absenteeism effects national economy. Indirect cost due to work lose and early retirement range from 20% and 69% of the total economic burden of COPD depending upon the social security policies of the countries (Rehman et al., 2020).

## 1.7 Problem Statement

Slowing down the progression of disease is an achievable goal in the management of COPD (ur Rehman et al., 2019). Spirometry test quantified as post bronchodilator forced expiratory volume in 1 second (FEV1) is most reliable and reproducible measurement of lung impairment and airflow limitation under the influence of COPD (GOLD, 2019). Current diagnosis system rely on it as an indicator of COPD disease progression. In addition to spirometric values, Global Initiative for Chronic Obstructive

Lung Disease (GOLD) 2019 updates recommend to assess impact of COPD on the health status of patients, disease progression rate and exacerbation frequency to categorize patients and propose a particular pharmacological therapy (Mannino et al., 2006). Incorporating health status questionnaires into the clinical investigations of COPD may aid in determining the treatment efficacy, disease severity and quality of life of COPD patients (Jones et al., 1994). Translation and validation of a health status measure to be used in clinical practice to assess symptoms severity and determination of risk factors responsible for decline in $FEV_1$ can help the health care professional to improve the management of COPD by directing resources to the ones in need, reduce progression of disease, reduce exacerbation and improve patient care (Celli et al., 2004).

COPD also results in significant economic burden to the patient and society resulting from productivity losses due to compromised quality of life. Among working age patients COPD is the 11th leading cause of work productivity loss and is expected to be $7^{th}$ until 2030. Despite being a major health problem, existing data on the economic burden of COPD in Malaysia is limited.

## 1.8 Objectives of the study

The objectives of our study were as follow

I. To develop a Malaysian version of SGRQ-C (SGRQ-CM) to assess the health status, quality of life and symptoms burden of COPD patients.

II. To evaluate the full spectrum of psychometric properties (reliability, validity and responsiveness) of the Bahasa Melayu translated version of SGRQ-C (SGRQ-

CM), to test the factor structure of SGRQ-CM and to assess MCID for the SGRQ-CM, to be used in the population of Malaysia.

III. To investigate the effect of different factors responsible for rapid deterioration of lung function quantified as decline in $FEV_1$ over time.

IV. To assess the economic burden of COPD in Malaysia, including direct costs for the management of COPD and indirect costs due to productivity losses of COPD patients.

## 1.9 General Objectives

The general objective of the study was to assess the economic burden of COPD, validate the SGRQ-CM as quality of life assessment tool and find the possible reasons of $FEV_1$ decline in COPD patients.

## 1.10 Significance of the study

- Translation and validation of SGRQ-C to Malaysian language and culture to measure in detail the four main domains of health status that include physiological functioning, symptoms, functional impairment, and HQOL.

- Translation and validation of SGRQ-C can help to assess the detailed symptomatic effect of disease and impaired HQOL among COPD patients in clinical practice and research studies.

- Translation and validation of SGRQ-C to Malaysian language can help in better management of COPD patients.

- To be used as endpoint in future therapeutic interventions clinical trials involving Malaysian population.

- Identify risk factors for rapid deterioration of lung function can help to design specific treatment strategies for patients on higher risk of lung function of deterioration to reduce the risk of lung function decline.

- Monitoring of economic burden, to keep health policy, clinical practice and research priorities up-to-date.

- Calculation of economic burden can help the health care professionals and policymakers to plan efficient and cost effective use of resources.

- Assessing the cost of management of COPD in a public hospital in Malaysia can help policy makers and government agencies with cost efficient allocation of resources for the management of disease and to find the key cost drivers and possible cost reduction areas in cost conscious environment.

- Dissemination of the findings to those who need to know and providing feedback to the management at health facilities and the Ministry of Health, Malaysia.

## 1.11 Thesis Overview

This thesis explores some important information related to validation of SGRQ-C to assess health status, risk factors associated with rapid deterioration of lung function and economic burden of COPD patients. This thesis comprise of seven chapters including

introduction, literature review, methodology, validation of SGRQ-C, Risk factors for decline in FEV1, economic burden of COPD in Malaysia and conclusion. The complementary information is added as appendices at the end of the thesis. Chapter one is introduction which contains brief introduction about COPD (prevalence and management), multidimensional assessment approach in GOLD and its importance in management of COPD, economic burden of COPD, problem statement, objectives of the study and significance of the study. The 2nd chapter is "literature review". It sheds light on the importance of SGRQ-C validation and $FEV_1$ decline for GOLD multidimensional assessment approach, past work done for validation of SGRQ-C, assessment of risk factors of $FEV_1$ decline and Global burden of COPD. 3rd chapter covers the brief methodology as detailed methodologies for each objectives are discussed in respective chapters. Chapter 4 is about translation and validation of SGRQ-C in Malaysia. It sheds light on importance of health status measure, why validation of SGRQ-C needed in Malaysia, methodology implied, results and discussion. Chapter 5 is about the risk factors associated with decline in lung function. It includes importance of $FEV_1$, gaps in previous research, methodology implied, results and discussion. The 6th chapter gives details about the economic burden of COPD in Malaysia and the methodology implied to evaluate the economic burden. The last chapter (7th) concluded the results of current study and future recommendations for research based on current study. The appendices contain the supplementary material which include ethical approval of this study, permissions obtained from different bodies related to this study, questionnaire used and the list of research publications from this study.

# CHAPTER 2

# LITERATURE REVIEW

## 2.1 Introduction

Quality of life (symptoms burden) and $FEV_1$ decline are two important factors of the multidimensional assessment system by Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines (GOLD, 2019). This novel multidimensional approach recommend the assessment of COPD patients based on the severity of symptoms, degree of airflow limitation and risk for future events to categories COPD patients in four groups (A, B, C and D) and propose a particular pharmacotherapy (GOLD, 2019). Symptoms severity is assessed with the help of health status measures (mMRC, CAT or SGRQ-C), degree of airflow limitation is assessed as $FEV_1$% value, while risk for future exacerbation is assessed as exacerbation frequency or $FEV_1$ decline, whatever results in a higher risk. Increase in symptoms burden (worsening quality of life), decline in $FEV_1$ or increase in exacerbation frequency can result in progression of COPD from acute to severe GOLD group. ECLIPSE study demonstrated that during one year period, 36% COPD patients remained stable in the same COPD severity group, 42% patients progressed to next group and 22% patients improved to lower severity group. The major reason of progression to the next group were decline in $FEV_1$ or reduced quality of life due to increase in symptom load or increase in exacerbation frequency (Vestbo et al., 2011). Both of these are also used as endpoints in various clinical trials to assess the effectiveness of different pharmacological and non-pharmacological interventions on COPD patients (Jones et al., 2016). Current pharmacological therapy for COPD focus on improving the quality of life of COPD patients, reducing the rate of decline in $FEV_1$ and exacerbation frequency. The

European law requires to add quality of life in addition to clinical measures as an endpoint in clinical trials of new drugs (Jones et al., 2016).

Factors that affect the rate of decline in $FEV_1$ are of keen importance in management of COPD. Available pharmacological therapies may not inhibit the decline in $FEV_1$ but can substantially reduce the rate of decline in $FEV_1$ in COPD patients (ur Rehman et al., 2019). Factors responsible for rapid decline in lung function may help to identify patients at high risk of lung function deterioration and taking on time measures (pharmacological or non-pharmacological treatment) to prevent rapid deterioration by resolving the risk factors (Hoesein et al., 2011). In addition to early risk stratification, patient reported outcomes (health status questionnaires) may assist spirometry test in assessing the true impact of disease on an individual. A systematic review have been done to assess the use of SGRQ-C as a validated questionnaire to determine the quality of life of COPD patients and to identify risk factors responsible for progression of $FEV_1$ in COPD patients.

## 2.2 Literature Search

The systematic review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Liberati et al., 2009).

We conducted a systematic search of PUBMED, SCIENCE DIRECT, SCOPUS, GOOGLE SCHOLAR and SAGE Premier Databases between 1976 (first study found) until June 20, 2020 (date last searched). Two separate search strategies were applied to find published scientific research articles for validation of SGRQ in different populations and articles determining the risk factors for decline in $FEV_1$.

To find SGRQ validation studies, search terms used in PUMBED were: SGRQ in combination with “Pulmonary Disease, Chronic Obstructive”, “emphysema”, “bronchitis”, airways obstruction, “obstructive lung disease”, “SGRQ-C”, “validation”, “psychometric analysis” and “quality of life”. To find studies about risk factors for decline in $FEV_1$, search terms used in PubMed were “decline in $FEV_1$” in combination with “Pulmonary Disease, Chronic Obstructive”, “emphysema”, “bronchitis”, airways obstruction, “obstructive lung disease”, “lung function decline”, “progression of COPD”, “prognosis”, “exacerbation” and “comorbidities”. Additional publications were identified by reviewing reference lists of included studies and consulting expert review articles identified through the search. The search was limited to publications in English language.

### 2.2.1 Inclusion and exclusion criteria

Two reviewers independently screened the titles and abstracts and recruited the original studies which fulfil the following inclusion criteria; (i) clearly identified COPD subjects according to WHO-ICD (ICD-9, ICD-10) or GOLD guidelines, (ii) original research exploring the single or multiple risk factors of decline in lung function ($FEV_1$) in COPD (iii) original research validating the SGRQ/SGRQ-C to assess quality of life of COPD patients, (iv) full text available through University Sains Malaysia’s library access or on request to the author, and (v) studies published between 1976 and June 20, 2020. Commentaries, letters to editors, editorials, posters or abstracts presented at scientific conferences, studies evaluating impact of specific therapy, studies involving pharmacological or non-pharmacological interventions and narrative review articles were not included in the systematic review. Studies recognized as potentially relevant were