Usefulness of Modified Medical Research Council (MMRC) Dyspnea Scale for Assessment of Dyspnea Severity in Clinical Practice in COPD patients

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ABSTRACT

Dyspnea is a predominant symptom of chronic obstructive pulmonary disease (COPD), and it considered as a major index of the disease severity and a prominent target of the treatment but its assessment is complex in clinical practice. The modified Medical Research Council scale (mMRC scale) is largely used in the assessment of dyspnea in chronic respiratory diseases. Aims of study to evaluate usefulness of mMRC (modified medical research council) for assessment of dyspnea severity in clinical practice in patients with COPD. Cross sectional study was carried out in AL-Emamain Al-Kadhimain medical city from 1st July 2018 to end of January 2019 hundred patients with COPD were included in this study. The sociodemographic and clinical history that related to admission to emergency and hospital wards at the last year and smoking status were recorded. Dyspnea was evaluated by the mMRC scale and classified according to spirometric measurements. 100 patients with COPD were included, mean age of the patients was 63±9.0, 80% was males and 20% was females, the mean of BMI was 27.1±5.05, 54% was current smoker and 46% was ex-smoker. The mean value of FEV1 for our patients was 55.4(GOLD2) and the mean value of SPO2, FEV1 and other parameters of spirometric findings were decreased significantly with progression of mMRC grade. Frequency of patients with late grades of mMRC had higher frequency of admission to emergency ward than hospital wards. The highest percentage of patients (32%) was in grade 2 according to mMRC and GOLD 2(50%) and there was significant association between mMRC grade and gold grade. Study shows that mMRC is useful scale for assessment the dyspnea intensity in patients with COPD.

1. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the most important cause of morbidity and mortality, currently it's the fourth leading cause of death in world [1]. COPD is the result of complex interplay of the long term. cumulative exposure to the noxious gases and particles, combined with variety of host factors

that include: genetics, airway hyper responsiveness and poor lung growth during the childhood period [2]. The prevalence of COPD is related to prevalence of the tobacco smoking, outdoor, occupational and indoor air pollution are major risk factors [3]. The prevalence of the COPD grade 2 or higher is 10.1% as overall, 11.8% for men, and 8.5% for women and a prevalence of COPD of 3-11% among the never- smokers [4]. Globally there are about 3 million deaths annually [5]. Morbidity of COPD include physician visits, visits to emergency department or hospitalizations. COPD databases of these outcome parameters are less available and less reliable than the mortality databases, to date the studies on available data indicate that morbidity from COPD increases with age, and the development of comorbidities may be seen at earlier age [6], [7]. The COPD should be considered in a patient with chronic cough, sputum, dyspnea, with history of exposure to the risk factors of the disease. Spirometry is required to make the diagnosis in this clinical context [8]. Goals of the COPD assessment to determine the level of airflow limitation, with its impact on a patient's health status and risk of the future events (as exacerbations, hospital admissions or death), in order to, guide therapy [1]. A simple measure of dyspnea such as the Modified British Medical Research Council (mMRC) scale considered adequate for the assessment of this symptom, as the mMRC relates well to the other measures of health status [9] and predicts future mortality risk [10]. The MRC scale was originally categorized into 5 grades, range from 1 (normal) to 5 (too dyspneic to leave the house). Then the ATS published a revised version, which designated the mMRC scale, as the dyspnea grades range from 0 to 4. This revised scale focused on dyspnea that occur during walks. Because this scale evaluates only the dyspnea that related to the specific activities, the scale does not allow the multidimensional evaluation of dyspnea. Also the mMRC scale does not detect changes in the degree of dyspnea after the therapeutic intervention [11]. However the mMRC scale is easy-to-use with no time consuming, it based on five statements describing almost the entire range of dyspnea in the daily living [12].

2. Methods

2.1 Study design and setting
A cross sectional study was carried out on a sample of 100 patients with COPD who were attended to respiratory unit of Al-Emamien Al-Kadhimiam Medical City from 1st July 2018 to end of January 2019.

2.2 Data collection
Well-developed questionnaire was used for collection of following data via direct interview and examination of the patients.
Sociodemographic charecteristics such as age, gender etc.
Smoking status that defined according to WHO definition, 2009 that defined ex-smoker as that adults who are ever daily tobacco smokers and currently do not smoke tobacco [12]
History of admission to the emergency in the last year
History of admission to the hospital in the last year
Grade and Gold grade were recorded according to the results of MMRC scale and spirometry findings

The mMRC dyspnea scale is a questionnaire that consists of five statements about perceived breathlessness: grade 0, "I only get breathless with strenuous exercise"; grade 1, "I get short of breath when hurrying on the level or up a slight hill"; grade 2, "I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level"; grade 3, "I stop for breath after walking 100 yards or after a few minutes on the level; grade 4, I am too breathless to leave the house or I am breathless when dressing or undressing " [1].

2.3 Inclusion criteria

Patients with COPD who diagnosed clinically and by pulmonary function test

2.4 Exclusion criteria
COPD exacerbation

2.5 Ethical issue, approval and official permission
Prior to data collection, the study protocol was reviewed; approval and official permission were obtained from the concerned authorities

2.6 Statistical Analysis
Statistical Package for the Social Sciences (SPSS) version 23 was used for data entry and analysis. Appropriate tests were used to confirm significance. The p≤0.05 was considered significant.

3. Results
The results of current study showed that the mean age of the patients was 63±9.0, 80% was males and 20% was females, the mean of BMI was 27.1±5. 05,54% was current smoker and 46%was ex-smoker as seen in table 1.

Table 1. Socio-demographic characteristics of patients

|		Mean	%
Age/year		63±9	
Gender	Female	20	20
	Male	80	80
BMI		27.1±5	
Smoking status	Ex-smoker	46	46
	Smoker	54	54

According to MMRC scale assessment, the results demonstrated that the highest percentage (32%) of our patients was classified at grade 2 of the disease, followed by grade 1(30%), grade 3(23%), grade 0(8%) and grade 4(7%). The results showed that 75% of the patients had history of admission to emergency ward at the last year and 47% had history of admission to the hospital in the last year. The mean value of spo2, FEV1, FVC, FEV1/FVC ratio, FEF 25, 50, 75% were 92.55±2.5, 55.45±17.4, 72.12±20.3, 60.56±8.5, 39.61±16.5, 30.92±12.09 and 26.68 ±9.09 respectively. The highest frequency of patients was in gold 2(50%) followed by gold 3(32%), gold 1(11%) and gold 4(7%) as displaced in table 2 and figure 1, figure 2.

Table 2. Clinical characteristics of patients

		No.	%
mMRC scale	Grade 0	8	8
	Grade 1	30	30
	Grade 2	32	32
	Grade 3	23	23
	Grade 4	7	7
Hx of admission to the emergency In the last year	Yes	75	75
	No	25	25
Hx of admission to the hospital In the last year	Yes	47	47
	No	53	53
Mean ±SD			

Spo2 %	92.55±2.508
FEV 1	55.45±17.49
FVC	72.12±20.3
FEV1\FVC Ratio	60.56±8.57
FEF 25%	39.61±16.53
FEF 50%	30.92±12.09
FEF 75%	26.68±9.09
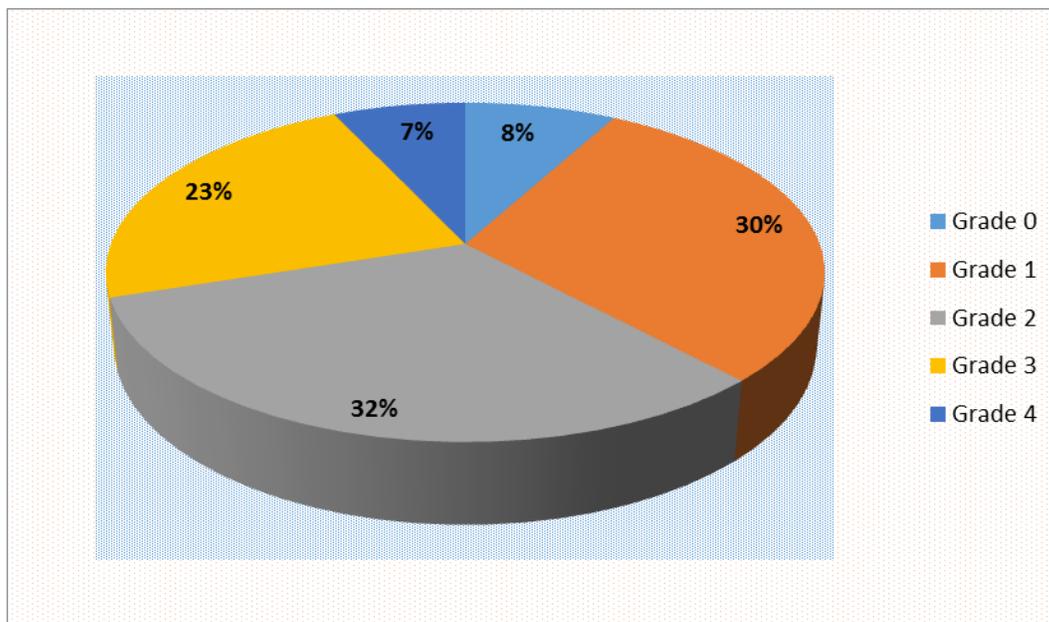
Figure 1. Distribution of patients according to MMRC grade.
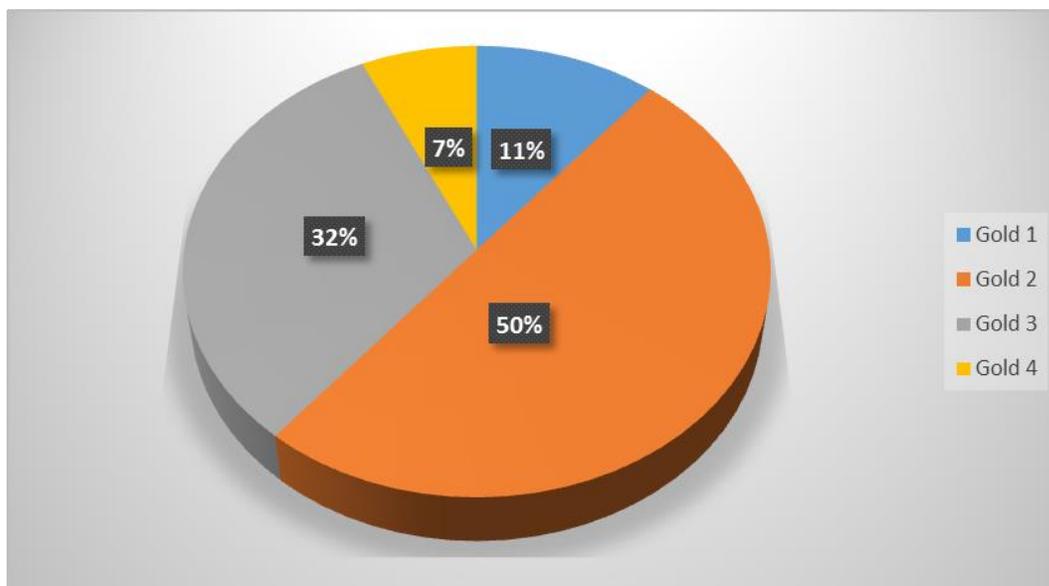

Figure 2. Distribution of patients according to GOLD grade.

The results revealed there was significant association between the history of admission to emergency unit or hospital and the patients grades as the results showed that all the patients with grade 3 and 4 had history of admission to emergency ward as well as high percentage of patients at grade 2 while those of grade 0 they

did not report any history of admission to emergency unit. Nearly similar findings was reported with history of admission to hospital but in percentages slightly lowered of what was reported with history of admission to emergency unit as illustrated in table 3.

Table 3. Association of MMRC scale and medical history of the patient's admission to ward and emergency unit at the last year

History of admission / last year		MMRC scale					P-value
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	
				No. (%)			
Emergency	Yes	0	15 (50)	30 (93.8)	23 (100)	7 (100)	0.001
	No	8 (100)	15 (50)	2 (6.3)	0	0	
Hospital	Yes	0	2 (6.7)	17 (53.1)	22 (95.7)	6 (85.7)	0.001
	No	8 (100)	28 (93.3)	15 (46.9)	1 (4.3)	1 (14.3)	
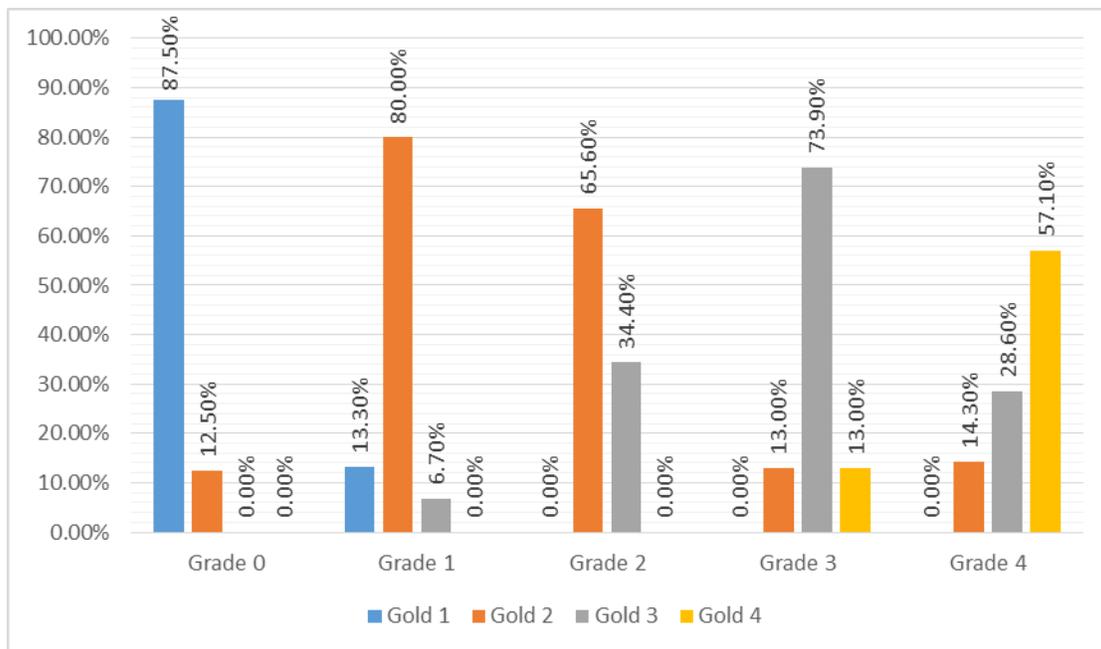
Figure 3. Association of MMRC scale and Gold grade of patients.

The results showed there was a significant association (p=0.01) between the grade of MMRC scale and gold grade where there was higher percentage of MMRC scale with grade 3 or 4 had reached the 3 or 4 of GOLD grade but no or smaller percentages of patients of grade 0, 1 according to MMRC scale had reached gold grade of 3 or 4 as seen in table 4.

Table 4. Association of MMRC scale and Gold grade of patients

MMRC scale	Gold grade				P value
	Gold 1	Gold 2	Gold 3	Gold 4	
Grade 0	7 (87.5)	1 (12.5)	0	0	
Grade 1	4 (13.3)	24 (80)	2 (6.7)	0	
Grade 2	0	21 (65.6)	11 (34.4)	0	0.01
Grade 3	0	3 (13)	17 (73.9)	3 (13)	
Grade 4	0	1 (14.3)	2 (28.6)	4 (57.1)	

The findings was demonstrated that the males and females patients distributed nearly in similar percentages according to each grade of MMRC scale which might be reflect the truth that the disease was progressed with males and females patients in similar manner as displaced in table 5.

Table 5. Association of MMRC scale and gender of patients

MMRC scale	Gender		P-value
	Female	Male	
	No. (%)		
Grade 0	2 (10)	6 (7.5)	
Grade 1	8 (40)	22 (27.5)	
Grade 2	6 (30)	26 (32.5)	0.7
Grade 3	3 (15)	20 (25)	
Grade 4	1 (5)	6 (7.5)	

The findings of current study also demonstrated that the ex –smoker and current smoker patients distributed nearly in similar percentages according to each grade of MMRC scale even that the percentages of current smoker patients that graded as 2 or3 among current smoker was higher than ex-smoker but the difference did not reach the significant level (p=0.1) which might be reflect the truth that the cessation of smoking may not improve the clinical status of the patients with COPD significantly as displaced in table 6.

Table 6. Association of MMRC scale and smoking status of patients

MMRC scale	Smoking status		P-value
	Ex -smoker	Smoker	
	No. (%)		
Grade 0	6 (13)	2 (3.7)	
Grade 1	16 (34.8)	14 (25.9)	
Grade 2	10 (21.7)	22 (40.7)	0.1
Grade 3	10 (21.7)	13 (24.1)	
Grade 4	4 (8.7)	3 (5.6)	

The results showed that the mean value of SPO2 was significantly lowered with progression of MMRC grades or progression of the disease as it was decreased from 94.75 with grade 0 to 89.57 with grade 4(p=0.001).The mean value of FEV1 also decreased significantly (p=0.001) with progression of MMRC grade where it was reduced from 84.11 with grade o to 31.05 with grade 4..The FVC was decreased from 93.6 with grade 0 to 41.65 with grade 4 and this difference was statistically significant(p=0.001).The FEV1/FVC ratio was significantly decreased(p=0.004) from 70.18 with grade 0 to 57.6.The FEF 25,50 and 75% were also reduced significantly(p=0.001 for all) from grade 0 to 4 as they were decreased from 69.13 to 18.57 , 50.12 to 14.57, 29.25 to 14.42, respectively, as illustrated in table 7.

Table 7. Association of MMRC scale and spirometric parameters and spo2

		No.	Mean±SD	P-value
Spo2 %	Grade 0	8	94.75±1.38	0.001
	Grade 1	30	94.37±1.65	
	Grade 2	32	92.63±1.54	
	Grade 3	23	90.22±1.85	
	Grade 4	7	89.57±3.04	
FEV 1	Grade 0	8	84.11±6.49	0.001

	Grade 1	30	66.53±10.71	
	Grade 2	32	54.47±11.11	
	Grade 3	23	39.8±9.36	
	Grade 4	7	31.05±11.95	
FVC	Grade 0	8	93.06±8.32	0.001
	Grade 1	30	84.99±11.14	
	Grade 2	32	73.29±17.07	
	Grade 3	23	55.7±16.06	
	Grade 4	7	41.65±11.6	
FEV1\FVC Ratio	Grade 0	8	70.18±2.69	0.04
	Grade 1	30	61.87±6.85	
	Grade 2	32	59.82±8.67	
	Grade 3	23	57.44±9.39	
	Grade 4	7	57.6±8.99	
FEF 25%	Grade 0	8	69.13±15.68	0.01
	Grade 1	30	46.73±13.00	
	Grade 2	32	38.94±11.69	
	Grade 3	23	27.39±6.52	
	Grade 4	7	18.57±6.07	
FEF 50%	Grade 0	8	50.12±9.37	0.01
	Grade 1	30	37.66±7.79	
	Grade 2	32	30.4±9.78	
	Grade 3	23	21.15±5.31	
	Grade 4	7	14.57±4.35	
FEF 75%	Grade 0	8	29.25±7.66	0.01
	Grade 1	30	32.9±8.62	
	Grade 2	32	26.25±8.6	
	Grade 3	23	22±4.86	
	Grade 4	7	14.42±2.5	

4. Discussion

In this study, the mean age of the patients was 63±9.0, this result is in agreement with [1], which showed that higher incidence in ≥ 40 year group compared to those < 40 also in agreement with [13], who were found that mean age of the COPD patients was 66.03±11.3 years and with [14], who reported mean age of 59.9±9.6 years old for COPD patients. Regarding gender in this study, 80% was males and 20% was females, also it is the similar result with [1], which showed that higher incidence found in men and also in consistent with who documented 61.4% of the patients with COPD were males and 38.6% were females [15]. The explanation of this difference may related to increase the exposure of males to risk factors such as smoking which is considered the most common risk factor for COPD. Regarding smoking status 54% was current smoker and 46%was ex-smoker was seen in this study, with no statistically significant difference between current and ex-smokers which might be reflect the truth that the cessation of smoking may not improve the clinical status of the patients with COPD significantly. In [16] study the Current/ex-smoker was 32 \ 68. While with [17], 79.2% of COPD patients were ex-smokers while 20.8% were active. This difference in results of this study and the previous studies may be due to the small sample number in this study. National Heart, Lung, and Blood Institute (2013) found that the COPD most often occurs in people with a history of smoking (either current or former smokers) [18]. In a meta-analysis of 55,079 individuals assessed at least twice with spirometry, it observed that women with history of smoking had a more rapid decline in the lung function

between ages of 45 to 50 years compared with men who are smokers [19]. The experimental studies indicate that estrogen may account for increased the susceptibility of women through its effect on TGFβ release in the small airways leading to fibrosis [20], [21]. Increasing in tobacco use in women is likely explains some of the increase in prevalence of COPD in women, however data suggests women may be actually at greater risk of the smoking-induced impairment in lung function, severe dyspnea, and poorer health status for same level of tobacco exposure. The degree to which these studies represent the biological, physiological, or sociological differences are not know yet [19].

The mean of BMI in this study was 27.1±5.05, study [22] showed that BMI in patients with COPD is 22.7 ± 4.1.

According to mMRC scale assessment, the results demonstrated that the highest percentage (32%) of our patients was classified at grade 2, and the lowest percentage (7%) was classified at grade 4. The results showed there was a significant association (p=0.01) between the grade of MMRC scale and gold grade where there was higher percentage with grade 3 or 4. Were found that the most of the patients were in mMRC grade 3 (40.38%) and only 15 (5.76%) patients had dyspnea of grade 4 [23]. The findings of this study also demonstrated no significant difference between males and females patients when the dyspnea graded according to mMRC scale as the percentage of males and females were distributed nearly in similar percentages with all grade of mMRC and no significant association was reported between the grade of mMRC scale and the gender of the patients which mean that the mMRC scale are useful in point that the COPD disease progressed in both gender in the same manner. Our results are in consistent with the report of Thoracic American Society [24] that deny the association of dyspnea with gender of the patients but in disagreement with that shown the female's patients significantly more perceive dyspnea than men with COPD, this difference may due to small number of female in our study [25]. The use of appropriate measurement tools, and understanding the determinants of dyspnea may be helpful for the clinician in management of the patients. Absence of the gold standard for assessment of dyspnea has been underlined. The study which compared mMRC, BDI, and the oxygen cost diagram concluded that these tools were valuable in the assessment of COPD status but mMRC remains the standard tool for evaluation of dyspnea in daily practice, in addition for its usefulness is highly emphasized in a new GOLD document [1]. The suggested cut-off to define significant symptoms was setting at grade 2, the recent data suggested that patients with mMRC grade 1 may already exhibit significant impact of COPD, as assessed by COPD assessment test (CAT) score [26]. The mMRC scale has advantage of being easy to perform and can be associated with clinically important variables [27].

Our data demonstrated that 75% had history of admission to emergency ward and 47% had history of admission to hospitals ward in the last years and the results showed that all the patients with grade 3 and 4 of mMRC had history of admission to emergency ward but had lower frequency of admission to hospital wards. This result was similar to [28] who stated that, hospitalization rates in COPD patients of late grade according to mMRC are high also similar to [13] who confirmed this results. The results showed that the mean value of SPO_2, FEV_1, FVC, FEV_1/FVC ratio and FEF25, 50, 75% were significantly decreased as the grade of the disease was progressed and these findings indicates that the patients of grade 3and 4 according to mMRC and late grade on gold assessment which indicate that this questionnaire is an important tool in the assessment of severity of dyspnea .This findings in agreement with [29] who has been found that the patients with late grades on mMRC dyspnea scale have moderate to severe COPD, also in consistent with the results of the studies that conducted by [30], [31] that confirmed our significant association between gold grade and mMRC grades. Other studies were showed that mMRC score correlated more strongly with the health-related quality of life, and with indices of anxiety and depression than with spirometric values [32], [33].

Determinants of dyspnea still poorly understood in COPD patients due to the complexity of this symptom and its individual variability for same level of physiologic impairment, for instance FEV1. Moderate relationship with the spirometry previously found using both the mMRC and BDI scores, although overall dyspnea scores are deteriorate significantly with the GOLD stages. The GOLD 2011 recommended the CAT or mMRC scores to distinguish the symptom groups (high vs low symptoms). Also the GOLD mentioned that it's unnecessary to use more than one symptom scale. Group assignment of COPD patients by each symptom scale, was different. The symptomatic cut point to differentiate the symptom groups, GOLD proposed either CAT score of 10, or mMRC score of 2.

5. Conclusion

This study showed that MMRC scale can be used to evaluate the dyspnea intensity in patients with COPD. There was a significant association between the grades of MMRC scale and the GOLD grades. A significant association between MMRC scale, Spo2 and spirometric parameters. No significant association between gender of patients and the MMRC scale.

The financial implication or other relations that can generate conflicts of interest.
None

Ethic committee aproval - original papers
By Al-Kadhimiya Teaching Hospital

Conflict of interest statement
None

Statement of human and animal rights
None

Informed consent declaration – original papers
None

6. References

[1]   Global initiative for chronic obstructive pulmonary disease, Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease, 2019 report. Available from: www.goldcopd.org

[2]   Lange P, Celli B, Agusti A, et al. Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease. N Engl J Med 2015; 373(2): 111-22.

[3]   Eisner MD, Anthonisen N, Coultas D, et al. An official American Thoracic Society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010; 182(5): 693-718.

[4]   Lamprecht B, McBurnie MA, Vollmer WM, et al. COPD in never smokers: results from the population - based burden of obstructive lung disease study. Chest 2011; 139(4): 752-63.

[5]   Global Burden of Disease Study Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global

Burden of Disease Study 2013. Lancet 2015; 385(9963): 117-71.

[6]   Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. Eur Respir J 2006; 28(3): 523-32.

[7]   Menezes AM, Perez-Padilla R, Jardim JR, et al. Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. Lancet 2005; 366(9500): 1875-81.

[8]   Buist AS, McBurnie MA, Vollmer WM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet 2007; 370(9589): 741-50.

[9]   Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 1999; 54(7): 581-6.

[10]   Sundh J, Janson C, Lisspers K, Stallberg B, Montgomery S. The Dyspnea, Obstruction, Smoking, Exacerbation (DOSE) index is predictive of mortality in COPD. Prim Care Respir J 2012; 21(3): 295-301

[11]   Ries AL. Impact of chronic obstructive pulmonary disease on quality of life: the role of dyspnea. Am J Med. 2006; 119(10 Suppl 1):12-20

[12]   Claire Launois et al. The modified Medical Research Council scale for the assessment of dyspnea in daily living in obesity: a pilot study BMC Pulmonary Medicine201212:61

[13]   Tel H., Bilgiç, Z., & Zorlu, Z. (2012). Evaluation of Dyspnea and Fatigue among the COPD Patients, Chronic Obstructive Pulmonary Disease - Current Concepts and Practice. Available at: http://www.intechopen.com/ books/chronic obstructive pulmonary-disease

[14]   Holm K E, MPH, Plaufcan M R, Ford D E et al. The Impact of Age on Outcomes in Chronic Obstructive Pulmonary Disease Differs by Relationship Status J Behav Med. 2014; 37(4): 654–663.

[15]   Wehieda SM, El-Sheikh AA, Sallam SA. Effect of Implementation of Teaching Modules about Physiological and Psychological Parameters on Expected Clinical Outcomes of Patients with Chronic Obstructive Pulmonary Disease 2017,6(5): 370-381

[16]   Demosthenes Makris, Nikolaos Tzanakis, Joanna Moschandreas et al. Dyspnea as sessment and adverse events during sputum induction in COPD. BMC Pulmonary Medicine 2006, 6:17

[17]   Faryniarz, K. Tomlinson D et al.: Impact of dyspnea and physiologic function of general health status in patient with COPD, Chest.1992; 102(2):395-401

[18]   National Heart, Lung, and Blood Institute. (2013): COPD are you at risk? [Last updated 2011 Sept; accessed 2013 Feb 11.

[19]   Han MK, Postma D, Mannino DM, et al. Gender and chronic obstructive pulmonary disease: why it matters. Am J Respir Crit Care Med. 2007; 176(12):1179-1184.

[20]   Gan WQ, Man SFP, Postma DS, Camp P, Sin DD. Female smokers beyond the perimenopausal period are at increased risk of chronic obstructive pulmonary disease: a systematic review and meta-analysis. Respir Res. 2006;7(1):52-52.

[21]   Barnes PJ. Sex differences in chronic obstructive pulmonary disease mechanisms. Am J Respir Crit Care. 2016; 193(8):813-814.

[22]   Sunmin Kim, Jisun Oh, Yu-Il Kim. Differences in classification of COPD group using COPD assessment test (CAT) or modified Medical Research Council (mMRC) dyspnea Scores: a cross-sectional analyses. BMC Pulmonary Medicine 2013, 13:35

[23]   Bhanurekha.B1, Sasisekhar T.V.D2, Saireddy Y et al. Correlation of MRC Dyspnoea Scale and Forced Expiratory Volume in First Second (FEV1) In Chronic Obstructive Pulmonary Diseases. Journal of Dental and Medical Sciences 2013, 7, 55-57.

[24]   Thoracic American Society: Dyspnea. Mechanisms, assesment and management: a consensus statement, Am J Respir Crit CareMed 159: 321-340, 1999.

[25]   Torres, J.P. Casanova, C. Garcini, A.M. et al. Respiratory factors associated with dyspnea in woman with COPDCongres 2006;806S: E4663

[26]   Arnaudis B, Lairez O, Escamilla R, et al. Impact of chronic obstructive pulmonary disease severity on symptoms and prognosis in patients with systolic heart failure. Clin Res Cardiol. 2012;101(9):717–726

[27]   Kim S, Oh J, Kim YI, et al. Differences in classification of COPD group using COPD assessment test (CAT) or modified Medical Research Council (mMRC) dyspnea scores: a cross-sectional analyses. BMC Pulm Med. 2013; 13:35.

[28]   Baghai–Ravary, R., Quint, JK., Goldring, JJP., Hurst, JR., Donaldson, GC.,& Wedzicha, JA. (2009): Determinatnts and impact of fatigue in patients with chronic obstructive pulmonary disease. Respiratory Medicine, Vol.103, pp.216-223.

[29]   Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T; Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. American journal of respiratory and critical care medicine, 2003; 167(4): 544-549.

[30]   Mahler DA, Rosiello RA, Harver A, Lentine T, McGovern JF, Daubenspeck JA. Comparison of clinical dyspnea ratings and psychophysical measurements of respiratory sensation in obstructive airway disease. Am Rev Respir Dis. 1987; 135(6):1229–1233.

[31]   Sanchez O, Caumont-Prim A, Gillet-Juvin K, et al. Activity-related dyspnea is not modified by psychological status in people with COPD, interstitial lung disease or obesity. Respir Physiol Neurobiol. 2012; 182(1):18–25.

[32]   Schlecht NF, Schwartzman K, Bourbeau J. Dyspnea as clinical indicator in patients with chronic obstructive pulmonary disease. Chr Respir Dis. 2005;2:183–91

[33]　　Hajiro T, Nishimura K, Tsukino M, Ikeda A, Oga T, Izumi T. A comparison of the level of dyspnea vs disease severity in indicating the health-related quality of life of patients with COPD. Chest. 1999; 116:1632–7.