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Original Article

Role of Different Physical Performance Tests in Predicting Severity of Chronic Obstructive Pulmonary Diseases Exacerbation

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ABSTRACT:

Background: Chronic obstructive pulmonary disease (COPD) is a prominent worldwide cause of mortality and morbidity. Lung function, generally represented as forced expiratory volume in one second (FEV1), is used to classify diagnosis and disease progression. Exercise intolerance is a significant impairment in COPD patients. Their capacity to do daily activities and their quality of life are greatly impacted by the condition. This study aimed to evaluate the ability of the five sit-to-stand (5STS), six-minute walk test (6MWT), and 4-meter gait speed (4MGS) test in predicting the severity of chronic obstructive pulmonary disease (COPD) exacerbations in stable COPD patients**. Methods:** This prospective cohort study was performed at Chest Administration, Faculty of Medicine, Zagazig University, and Ahmed Maher Teaching Hospital on 100 patients presenting with COPD. All selected participants were evaluated at baseline (T0) and after six months of thorough medical history, clinical examination, the classification of COPD exacerbation severity, ABG and spirometric PFT, the six-minute walking test, the five-repetition sit-to-stand test, and the 4MGS test were performed. **Results:** This survey demonstrated that the 4MGS test and the 6MWT had an extremely identical predictive destiny. While 5 STS showed the highest prediction values than 6MWT and 5STS. The 5STS test and 4MGS test are probably useful alternatives to the 6MWT for predicting the severity of COPD exacerbation. **Conclusions**: through patients with stable COPD, physical tests such as 6MWT, 5STS, and 4MGS can predict the assumption, frequency, and severity of acute exacerbation of COPD.

Keywords: Chronic obstructive pulmonary disease, six-minute walk test, 4-meter gait speed, five-repetition sit-to-stand.

INTRODUCTION:

Dyspnea, exhaustion, anxiety, and despair are just a few of the symptoms that define chronic obstructive pulmonary disease (COPD) **[1]**. These symptoms also correspond to a lower ability to exercise and a lower quality of life (QOL) **[2].**

With chronic obstructive pulmonary disease (COPD), exacerbations are common. Annually, patients with this illness may have one to four exacerbations **[3].** Persistent

worsening of respiratory symptoms is a hallmark of exacerbations, which hasten the deterioration of pulmonary function **[4].** They are thought to be a defining feature of COPD. In the event of a significant exacerbation, patients must be admitted to the hospital **[5].**

Exercise performance predicts unfavorable outcomes like death and captures the integrated and multi-systemic consequences of chronic obstructive pulmonary disease (COPD) **[6]**.

Finding factors linked to a high risk of exacerbations is a critical goal in clinical COPD management because of exacerbations' frequency and intensity. The history of exacerbations in prior years is the best predictor of mild to severe exacerbations. Advanced age and clinical traits including dyspnea, a lower forced expiratory volume in one second (FEV1), the number of comorbidities, and exercise ability are further factors **[7].**

Despite the validation of multiple laboratory-based and field diagnostics for COPD, certain limitations may hinder their general implementation in certain healthcare environments. Laboratory tests need specialized equipment, manpower, and space, and are costly and labor-intensive. Field walking tests are less complicated and more affordable, but they are still not frequently utilized in primary, acute, or home care settings because of their time and space constraints **[8].**

One often used technique to evaluate a patient's ability to tolerate exercise with COPD is the six-minute walk test (6MWT) **[9]**.

One frequent daily task that depends on balance and lower limb muscular function is the sit-to-stand (STS) motion **[10]**.

Because the 4-meter gait speed (4MGS) is easy to use, practical, and takes up little space, it can be used in both clinical and research settings to assess walking speed in patients with chronic obstructive pulmonary disease (COPD) **[11].** Therefore, to assess the validity and responsiveness of the six-minute walk test (6MWT), four-meter gait speed (4MGS), and five-repetition sit-to-stand (5STS) in patients with chronic obstructive pulmonary disease (COPD), we focused on their accuracy.

METHODS

This prospective cohort study was performed at Chest Administration, Faculty of Medicine, Zagazig University, and Ahmed Maher Teaching Hospital on 100 patients presenting with COPD during the period from August 2022 to January 2023 to evaluate the capability of the 5STS, 6MWT, and 4MGS test to predict severity of COPD exacerbations in stable COPD group. After protocol approval by our Local Ethics Committee (IRB # 9354-1-3-2022). To participate in the study, each patient gave written, informed consent. The study protocol complied with the Declaration of Helsinki's (1975) ethical standards for human subjects research.

Inclusion criteria were age >40. Individuals who met the guidelines of the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) and had stable COPD (at least for three months before study inclusion) [**12].** A post-bronchodilator FEV/forced vital capacity ratio of 0.7. Exclusion criteria; (patients unable to do 3 tests). Patients having a heart ailment that is unstable within the period before the start of the study. Patients with cognitive deterioration. Lower limb joint surgery.

All selected participants were evaluated at baseline (T0) and after six months by full medical history including age, gender, number of co-morbidities, smoking habits, BMI (kg/m^2), the number of exacerbations in the preceding year, classification of COPD exacerbation severity (Mild: treated with Short-acting bronchodilators only, SABAs. Moderate: treated with SABAs plus antibiotics and/or oral corticosteroids. Sever: patient requires hospitalization or visits the emergency room) **[1]**; and the dyspnea grade (as determined by the modified British Medical Research Council (mMRC) scale); a COPD assessment test (CAT); the resting oxygen saturation (SpO2) and an index GOLD stage.

Clinical examination includes General and local chest examination, especially the vital data (blood pressure, temperature, heart rate, respiratory rate). Arterial Blood Gas (ABG) and spirometric pulmonary function tests were performed.

Patients having different degrees of obstruction were added to the study, a low forced expiratory volume in first second/forced vital capacity (FEV1/FVC) ratio of less than 70% suggested an obstructive problem. If an obstructive defect was present, we determined if the condition could be reversed based on the rise in FEV1 with bronchodilator therapy (i.e., an increase of more than 12% or more than 200 ml in adults) to exclude bronchial asthma.

Technique:

The six-minute walk test [13]:

Before beginning the exam, the patient should take around ten minutes to rest. Take a baseline oxygen saturation and heart rate measurement. To find the lowest oxygen saturation, which could happen before the test is over, these should be continuously observed. After that, the Borg scale is used to rate the patient's baseline dyspnea. Set the timer and lap counter. Give the patient thorough instructions on how to behave throughout the examination. After that, the patient is placed at the beginning line and given the all-clear to walk once the test starts. Only during the test should the technician speak with the patient. The patient should be urged to finish the test by being informed of the remaining time as each minute goes by. Record the Borg dyspnea, heart rate, oxygen saturation, number of laps completed using the counter or worksheet markings, and total distance walked after the test. Two groups were created based on the results (<350 m or ⩾350 m), 350m was regarded as inadequate physical performance.

The five-repetition sit-to-stand test [14]:

It timed how long it took to get up five times as rapidly as possible from a seated posture in seconds. A 48 cm hard-seat chair was resting against a wall to preserve its floor-to-seat height. The subject was told to sit with two arms tucked from one side to another side through their trunk and their feet precisely placed on the ground, after which the researcher went over the necessary procedures and safety measures with them. The next instruction was for them to fully get up and sit down again without using their arms. This sit-to-stand exercise was to be repeated five times as fast as possible for the participant, and the time it took to finish each repetition was noted. The participant's score was calculated as the lowest number obtained after three 5STS trials. The test was over when the subject was requested to stop or was unable to complete the action. Three 5STSs were executed by the patients at the proper number of intervals (<5 minutes). The subject was asked if they were still fatigued after each interval. If the response was "no," the tests went on, and if the response was "yes," the individual would keep resting until they were no longer exhausted. Before beginning three 5STSs, breathlessness was measured using the Borg scale.

The 4MGS test [15].

It was done by two cones placed 4m separated, and the test was positioned right in front of the first cone, which served as the starting point. The patient's first movement began the timing, which ended when the patient's first foot fully passed the second cone. Participants were told to stroll along this hallway at their regular pace. (4MGS-4U protocol) and maximum (4MGS-4M protocol) pace.

Statistical analysis:

The SPSS software (Statistical Package for Social Science) version 26 was utilized to computerize and do statistical analysis on the gathered data. Using the Shapiro Walk test, data was examined for normal distribution. Relative percentages and frequencies were used to depict qualitative data. The standard deviation and mean were used to express quantitative data. To evaluate how effectively predictors can forecast exacerbations, an ROC (receiver operating characteristic) curve analysis was developed. A predictor with an AUC of 1 accurately classifies people as either living or dead. AUC = 0.5, on the other

hand, indicates that there isn't a noticeable difference in the predictor values between the two groups' distributions. The cut-point is the value that maximizes the function's overall potential cut-point values, which is the difference between the genuine positive rate and the false positive rate. P-value < 0.05 denotes a significant difference, whereas P≥ 0.05 denotes a non-significant difference.

RESULTS:

A total sample of 100 COPD patients was included in this study with a mean age of 59.9±11.1 years. Sixty-three percent were males. Among the Studded patients, 22% were current smokers, 41% were ex-smokers and 37% were none smokers. The mean MMRC was 2.0±1.5 among the Studded patients. There were 24% diabetic and 25% hypertensive. There 47% had one or two exacerbations. The mean CAT score was 20.9±10.7. About one-third of studied patients were graded 2 of the gold stage. Table 1 shows that 24% of studied patients had mild, 35% of studied patients had moderate, and 23% of studied patients had severe exacerbations. The mean 6 MWT was 313.4± 157.3. The mean 5 STS was 12.6± 5.2 and the mean 4 MGS was 19.9±8.4 as shown in Table 1.

Table 2; according to the GOLD classifications, 40.2% were grade 2 the mean FEV1 was 59.3±11.7, mean FEV1/FVC was 0.57± 0.13 after 6 months. After 6 months of follow-up, the mean 6 MWT was 276.7± 152.1. The mean 5 STS was 12.2±8.5 and the mean 4 MGS was 17.4±10.9.

Table 3; showed that there was a statistically significant indirect correlation between 6 MWT and the severity of exacerbation. While 5 STS and 4 MGS were statistically significant and positively correlated with severity of exacerbation.

Figure 1; showed that there was a statistically significant negative correlation between 6MWT and the severity of exacerbation.

Figure 2; showed that there was a statistically significant positive correlation between 5STS and the severity of exacerbation.

Figure 3; showed that there was a statistically significant positive correlation between 4MGS and the severity of exacerbation.

Table 4; Upon comparing the validity and accuracy of the three physical tests, 5 STS had higher sensitivity. 6 MWT with a score lower than 350 had a sensitivity of 78.9% and specificity of 61.7% for predicting the severity of COPD exacerbations. While 5 STS with a score equal to or lower than 7 seconds had 91.7% sensitivity and 60% specificity in comparison to 4 MGS with a score equal to or lower than 3 had a sensitivity of 75 % and specificity of 59 %.

Table 5; showed that a significant difference was found between patients with 6 MWT > 350 and patients with 6 MWT < 350 regarding CAT, number of exacerbations, and its severity. With significantly higher CAT scores and MMRC grade, frequent exacerbations and more severe exacerbations in patients with 6 MWT ≤350 m.

Table 6; showed that a significant difference was found between patients with 5 STS < 7 and patients with 5 STS > 7 regarding CAT, number of exacerbations, and its severity with significantly higher CAT score, MMRC grade, frequent exacerbations, and more severe exacerbations in patients with STS >7 sec.

Table 7; showed that a significant difference was found between patients with 4 MGS < 3.5 and patients with 4 MGS > 3.5 regarding CAT, number of exacerbations, and its severity with significantly higher CAT score, MMRC grade, frequent exacerbations, and more severe exacerbations in patients with MGS >3.5 sec.

Table (1): Demographic data of the study patients at baseline.

Variable		n= 100
Age (years)	Mean ± SD	59.9± 11.1
	Median (Range)	60 (40, 80)
Gender	Male, n (%)	63 (63)
	Female, n (%)	37 (37)
Smoking	Non-smoker, n (%)	37 (37)
	Ex-smoker, n (%)	41 (41)
	Current smoker, n (%)	22 (22)
MMRC	Mean ± SD	2.0± 1.5
	Median (Range)	2 (0, 4)
Comorbidity	No, n (%)	32 (32)
	Diabetes, n (%)	24 (24)
	HTN, n (%)	25 (25)
	Cardiac, n (%)	10 (10)
	Others	9 (9)
NO. of exacerbations (in the previous year)	0, n (%)	18 (18)
	1-2, n (%)	47 (47)
	≥3, n (%)	35 (35)
CAT	Mean ± SD	20.9± 10.7
	Median (range)	19 (7, 39)
GOLD	Grade 1, n (%)	26 (26)
	Grade 2, n (%)	30 (30)
	Grade 3, n (%)	23 (23)
	Grade 4, n (%)	21 (21)
Severity of exacerbation (in the previous year)	No exacerbations, n (%)	18 (18)
	Mild, n (%)	24 (24)
	Moderate, n (%)	35 (35)
	Severe, n (%)	23 (23)
6MWT (m)	Mean ± SD	313.4± 157.3
	Median (range)	326.5 (63, 558)
5 STS (sec)	Mean ± SD	12.6± 5.2
	Median (range)	11.5 (3, 28)
4 MGS (sec)	Mean ± SD	19.9± 8.4
	Median (range)	19.5 (5, 33)

Table (2): data of patients after 6 months:

Variable		n= 100
NO. of exacerbation (in last 6 months)	0, n (%)	22 (22)
	1-2, n (%)	34 (34)
	≥3, n (%)	44 (44)
Severity of exacerbation	No	22 (22)
	Mild	29 (29)
	Moderate	28 (28)
	Severe	21 (21)
CAT	Mean ± SD	18.3± 9.6
	Median (range)	18 (2, 35)
FVC of the Studded patients after 6 months /GOLD and FEV1, FEV1		n= 92
GOLD	Grade 1, n (%)	29 (31.5)
	Grade 2, n (%)	37 (40.2)
	Grade 3, n (%)	22 (23.9)
	Grade 4, n (%)	4 (4.3)
FEV1	Mean ± SD	59.3± 11.7
FVC/FEV1	Mean ± SD	0.57± 0.13
Physical performance tests of the Studded patients after 6 months		
6MWT (m)	Mean ± SD	276.7± 152.1
5 STS (sec)	Mean ± SD	12.2± 8.5
4 MGS (sec)	Mean ± SD	17.4± 10.9

Table (3): Correlation between severity of exacerbation after 6 months and physical performance tests.

Variables	r	P-value
6MWT (m)	-0.580	<0.001*
5 STS (sec)	0.725	<0.001*
4 MGS (sec)	0.702	<0.001*

Student t-test; Chi-square test; *p is significant at <0.05

Table 4. Sensitivity and specificity of the physical performance tests for prediction of severity of COPD exacerbation.

Variable	AUC	Sensitivity	Specificity	P value
6 MWT <350	0.766	78.9%	61.7%	<0.001
5 STS ≤ 7	0.74	91.7%	60%	<0.001
4 MGS ≤ 3	0.677	75%	59%	0.009

Student t-test; Chi-square test; *p is significant at <0.05

Table 5. Relation between baseline 6 MWT and CAT, No. of exacerbation, and severity of exacerbation after 6 months.

Variable		6 MWT >350 N=60	6MWT ≤350 N=40	P value
CAT score	Mean ± SD	12.5± 11.6	22.7± 8.5	<0.001*
MMRC	Mean ± SD	2.0± 1.5	3.2± 1.3	<0.001*
No. of exacerbation	0, n (%)	18 (30)	4 (10)	<0.001*
	1-2, n (%)	27 (45)	7 (17.5)	
	≥3, n (%)	15 (25)	29 (72.5)	
Severity of exacerbation	No	18 (30)	4 (10)	<0.001*
	Mild	20 (33.3)	9 (22.5)	
	Moderate	15 (25)	13 (32.5)	
	Severe	7 (11.7)	14 (35)	

Student t-test; Chi-square test; *p is significant at <0.05.

Table 6. Relation between baseline 5 STS and CAT, No. of exacerbation, and severity of exacerbation after 6 months.

Variable		STS >7 n= 63	STS ≤7 n= 37	P value
CAT score	Mean ± SD	21.5± 9.5	14.3± 9.6	<0.001*
MMRC	Mean ± SD	3.6± 1.5	2.2± 1.4	<0.001*
No. of exacerbation	0, n (%)	3 (4.8)	19 (51.6)	<0.001*
	1-2, n (%)	28 (44.4)	6 (16.2)	
	≥3, n (%)	32 (50.8)	12 (32.4)	
Severity of exacerbation	No	3 (4.8)	19 (51.4)	<0.001*
	Mild	21 (33.3)	6 (16.2)	
	Moderate	20 (31.7)	10 (27)	
	Severe	19 (30.2)	2 (5.4)	

Student t-test; Chi-square test; *p is significant at <0.05.

Table 7. Relation between baseline 4 MGS and CAT, No. of exacerbation, and severity of exacerbation after 6 months.

	Variable	MGS >3.5 69 n=	MGS ≤3.5 N= 31	P value
CAT score	Mean ± SD	21.5± 9.5	14.3± 9.6	<0.001*
MMRC	Mean ± SD	3.4± 1.4	2.1± 1.3	<0.001*
No. of exacerbation	0, n (%)	8 (11.6)	14 (45.1)	<0.001*
	1-2, n (%)	28 (40.6)	6 (19.4)	
	≥3, n (%)	33 (47.8)	11 (35.5)	
Severity of exacerbation	No	8 (11.6)	14 (45.1)	<0.001*
	Mild	19 (27.5)	8 (25.8)	
	Moderate	23 (33.3)	7 (22.6)	
	Severe	19 (27.5)	2 (6.5)	

*Student t-test; Chi-square test; *p is significant at <0.05*

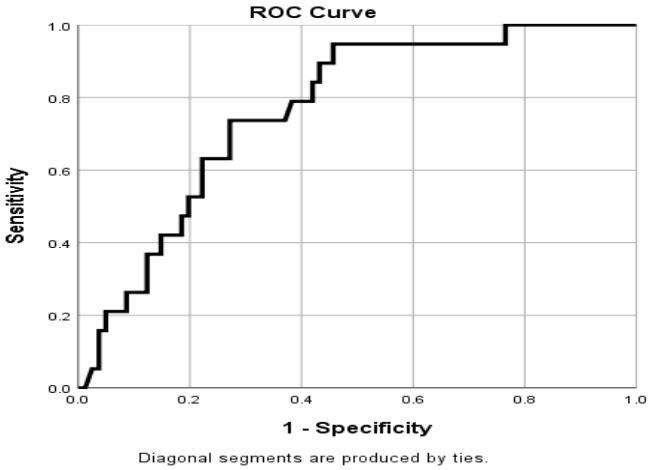

Figure 1: ROC curve analysis of 6 MWT to predict severity

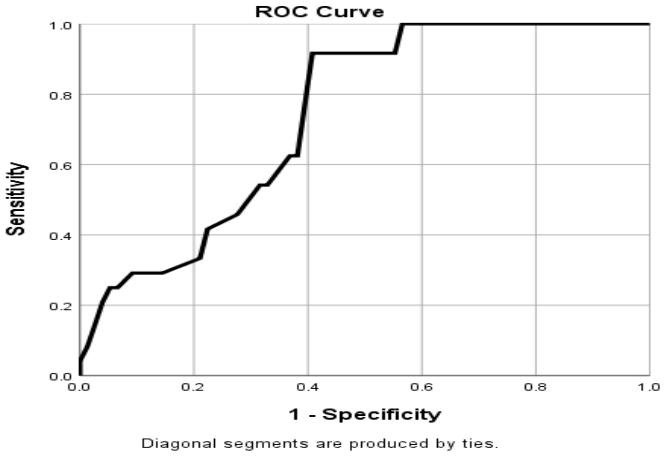

Figure 2: ROC curve analysis of 5 STS to predict severity.

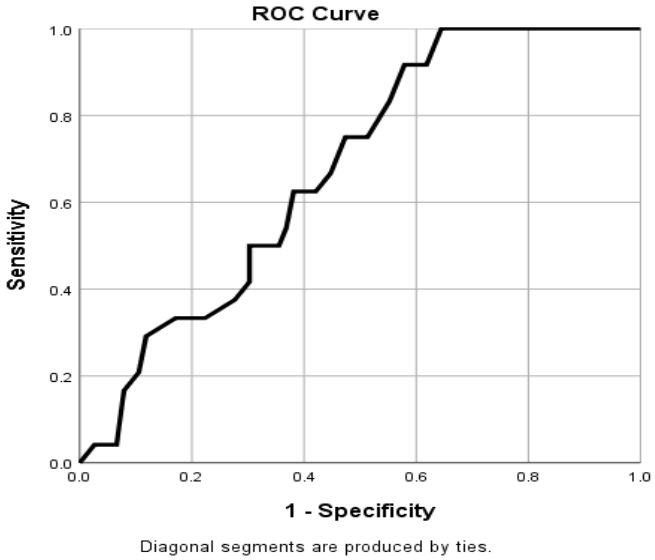

Figure 3. ROC curve analysis of MGS to predict severity.

DISCUSSION

One major clinical characteristic of a decreased tolerance to exercise in chronic obstructive pulmonary disease can be easily assessed using the 6-minute walking test (6MWT). Walking distance has been demonstrated to improve after COPD therapy treatments, such as surgeries involving lung volume reduction **[6]**.

The 6 MWT is the exam that is most frequently used to rate how functionally capable COPD patients are. This test evaluates a patient's ability to engage in functional activity despite having COPD and is valid, responsive, and dependable. Numerous illnesses, such as heart disease, neuromuscular disease, and obstructive lung disease, lower the 6MWD **[16]**.

The results of the investigation showed a statistically significant inverse relationship between 6MWT and the frequency and intensity of exacerbations.

Similarly, **Waatevik et al[17]** discovered a potential correlation between the number of exacerbations and the change in 6MWD. In actuality, the outcome indicates that declining >350m 6MWD in 1 year may be associated with many exacerbations over time.

Celli et al[18] they agreed that a 6MWD of 350 m chooses a cutoff point below which the likelihood of exacerbations rises noticeably.

Morakami et al[19] demonstrated that patients in Brazil can be predicted by the 6MWD to experience COPD exacerbations over two years. Within two years, patients who have experienced an exacerbation of their COPD are more than twice as likely to the 6MWD is ≤ 80% predicted.

The current study showed that 6 MWT with a score lower than 350 had a sensitivity of 78.9% and specificity of 61.7% (hier specificity) for forecasting the degree of exacerbations in COPD.

A study by **Andrianopoulos et al[20]** investigates the predictive usefulness of the six MWT-derived variables, such as six MWD, six MW Speed, and six MWT, for the prediction of hospitalization and death in patients with COPD over a three-year follow-up. Hospitalization prognosis may be influenced by the 6MWT due to severe exacerbation at a cut-off value ≤ 357 with a sensitivity of 54% and specificity of 62%.

Poor 6 MWD is influenced by a variety of complicated psychological and physical conditions, and a result of less than 350 meters is significant for prognosticating patients with high-risk COPD **[6]**.

Similarly, **Casanova et al[21]** demonstrated that the sensitivity of 6 MWT at a cut-off value of 350 61% and specificity of 70%.

These differences can be caused by the

deconditioning and prolonged inactivity of the peripheral muscles in individuals with COPD, which can lead to a decrease in their functional capacity. Furthermore, dyspnea and lower limb muscle weakness may be accompanied by cardiorespiratory restriction in these patients, which impacts performance outcomes.

In agreement, **Celli et al[18]** have out a study to determine the lowest clinically meaningful difference for change in 6MWD over one year as a function of mortality and initial hospitalization in an observational cohort of patients with COPD. The 5STS assesses the capacity to rise from a seated posture and is influenced by postural control, cardiorespiratory reserve, lower limb muscle strength, and balance. Above all, the STST is a useful and well-tolerated test that may be used in the majority of clinical situations, including the bedside **[22,23]**.

The results of this study showed that 5 STS was statistically significantly positively correlated with exacerbation severity and frequency.

Similar to our results, **Medina-Mirapeix et al[14]** showed that 5 STS was significantly associated with exacerbation severity. For COPD patients, the 5STS test was a significant, independent predictor of the chance of experiencing severe exacerbations in the upcoming year. Furthermore, the predictive powers and discriminatory accuracies of the 5STS and 6MWT tests are equivalent in identifying patients who were at a high risk of being admitted to the hospital.

A similar study was conducted by **Medina-Mirapeix et al[14]** to evaluate the efficacy of the 5STS and 4MGS tests' capacity to forecast severe exacerbations in stable COPD patients over the course of the next year, as well as the better prognostic test's ability to correctly recognize individuals at high risk of hospitalization. They concurred that among COPD patients, 6MWT was linked to severe exacerbations.

Similarly, **Kakavas et al[23]** concurred that the five-repetition sit-to-stand test performance time showed a middling capacity for exacerbation prediction. The number of exacerbations of COPD in the preceding year and, in the case of the 5STST time, the number of hospitalizations for COPD exacerbations in the previous year are substantially correlated with measurements obtained from the 5STST and 30s-STST.

According to this study, five STS with a score of seven seconds or less had 91.7% sensitivity (hier sensitivity) and 60% specificity for the prediction of the severity of COPD exacerbations.

Also, **Bernabeu-Mora et al[24]** demonstrated revealed the independent AUC (in seconds) of the 5STS test was 0.711 (95% confidence interval [CI] 0.613–0.809), at the cut of 13 seconds the sensitivity was 75.6% and specificity was 45.9%.

These discrepancies could be explained by the fact that the performance on the STS test represents a specific transfer ability and is influenced by many physiological and psychological processes in addition to lower limb muscular strength.

According to our results, 4 MGS was statistically significantly positively correlated with exacerbation severity.

In the same way, **Medina-Mirapeix et al[14]** showed that 4 MGS was significantly associated with exacerbation severity.

This study showed that 4MGS with a score equal to or lower than 3 seconds had 75% sensitivity and 59% specificity for the prediction of the severity of COPD exacerbations.

Similar results were obtained by **Kon et al[25]**, who showed that, even after controlling for all of the exacerbations that occurred in the previous year, the 4MGS remained a reliable predictor of exacerbations.

Comparable with **Bernabeu-Mora et al[24]** at cut-off ≤ 3 The 4MGS test demonstrated low discriminatory power (AUC <0.7), however when variables were taken into account, accuracy increased (0.726, 95% CI 0.637–0.816). The sensitivity was 79.6% and specificity was 49.4%.

While **Medina-Mirapeix et al[14]** revealed that individuals with 4MGS test results, according to unadjusted model results ≤ 3

(less functional) had a higher probability of experiencing exacerbations in the ensuing year. After the model's age and number of exacerbations were adjusted in the preceding year, this conclusion did not hold significance.

Ozsoy et al[26] The results demonstrated that in older COPD patients, Atypical functional exercise ability (sensitivity 85%, specificity 56%) and declining health status (sensitivity 90%, specificity 69%) were indicated by gait speeds of 0.96 m/s and 1.04 m/s, respectively.

The variation in reported cut-off values could be attributed to variations in sample populations and methodology. Inconsistencies in the declared threshold values may have their roots in variations in reference values and methods of administering tests.

This study found that patients with 6 MWT less than 350, 5 STS more than 7, and 4 MGS more than 3.5 experienced worsening and more frequent exacerbations. Moreover. Their CAT score and MMRC grade were higher.

The comparison of the three physical tests (6MWT, 5STS, and 4 MGS) in predicting the severity of COPD exacerbations in patients with stable COPD was one of this study's highlights.

CONCLUSIONS:

This study concluded that in individuals with stable COPD, physical tests such as 6MWT, 5STS, and 4MGS can predict the occurrence, frequency, and severity of acute exacerbation of COPD.

Conflicts of Interest

The authors report no conflicts of interest. The authors are responsible for the content and writing of the paper.

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None declared

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