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Relationship between cognition, disease severity and balance performance in individuals with Chronic Obstructive Pulmonary Disease

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ABSTRACT

Background: Accumulating evidence reveals that balance and cognitive impairment often coexist in individuals with Chronic Obstructive Pulmonary Disease (COPD), particularly in severe stage of COPD. However, the correlations among the disease manifestations remain uncertain. Understanding the contribution of disease severity and cognition to balance may lead to an optimal clinical assessment and intervention in this population.

Objectives: To examine the correlations between disease severity, cognitive function and balance performance in individuals with COPD.

Materials and methods: Fifty individuals with COPD aged 40 years and over participated in this cross-sectional study. Disease severity was evaluated using spirometry and classified according to the Global Initiative for Obstructive Lung Disease (GOLD). Cognitive performance was measured using the Montreal Cognitive Assessment-Basic (MoCA-B) Thai version. Balance performance was assessed using the Timed Up and Go test (TUG) under single- and dual-task conditions.Pearson's correlation coefficient was used to examine the relationship between the parameters evaluated. Independent sample student's t-test was conducted to compare balance performance between participants with and without cognitive impairment. Significance level was set at 0.05 for all analyses.

Results: The time taken to complete TUG for both single- and dual-task conditions was negatively correlated with the MoCA-B score (TUG-single r = -0.47; TUG-dual r = -0.48; $p \leq 0.001$). There were no correlations between the time to complete TUG both conditions and %predictedFEV1. Subgroup analyses demonstrated that the cognitively-impaired group took significantly longer time to complete TUG for both conditions than the cognitively-intact group ($p<0.01$).

Conclusion: Balance performance significantly correlated with cognitive performance but not COPD severity. Cognitive impairment adversely affected balance ability and posed individuals with COPD at risk of falls. Balance and cognitive performances should be assessed in individuals with COPD regardless of the disease severity.

Introduction

Chronic Obstructive Pulmonary disease (COPD), a respiratory disease that results in progressive airflow limitation, is a leading cause of morbidity, mortality, and health care expenditure worldwide. The prevalence of COPD has continued to increase and estimated to be the fourth leading cause of mortality by the year 2030.[1] Although the primary underlying pathophysiology is lung function, other systemic functions such as musculoskeletal

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and neuromuscular functions are affected in individuals with COPD. Thus, a wide range of impairments including muscle weakness, balance and cognitive impairments are presented in individuals with COPD.

Balance impairment is highly prevalent in individuals with COPD. Previous studies have demonstrated balance impairment across all stages of COPD severity.[2, 3] Lower limb muscle weakness, fatigue, and physical inactivity have often been reported to be associated with impaired balance in individuals with COPD.[4-6] Although central processing is essential for balance control[7], few studies have investigated the contribution of cognitive function to balance control in this population. Among several clinical tests, Timed Up and Go (TUG) test has been widely used to identify functional mobility, balance deficit, and risk of falls in healthy older adults and those with different medical diagnoses including COPD.[4, 8] Recently, the TUG dual task, adding either a cognitive or motor task, has often been used as previous research found that it increased the sensitivity to detect balance problem, consequently enhancing the ability to predict falls.[8, 9]

Cognitive impairment has been increasingly recognized in individuals with COPD. A large longitudinal study found that individuals with COPD had 4.2-fold increased odds of having mild cognitive impairment and 15.5-fold increased odds of having dementia compared to non-COPD.[10] Although a previous study suggested that the cognitive impairment in COPD is primarily relevant with hypoxia [11], non-hypoxemic COPD individuals also demonstrate cognitive impairment.[12] As both cognitive and balance impairments are independent risk factors for falls, balance and cognitive function are recommended as routine assessment in the elderly.[13, 14] These tests, however, are not yet routinely included in COPD population.

Taken together, accumulating evidence demonstrated that balance and cognitive impairment often coexist in individuals with COPD.[3, 10] However, the correlation of these disease manifestations remains unclear. Further, the severity of COPD has also been documented to influence balance impairment. Previous work found that COPD patients with severe to very severe stage (%predictedFEV_1< 50%) demonstrate greater balance impairment than those with mild stage (%predictedFEV_1 ≥80%).[2] Therefore, the aim of this study was to determine the correlations between cognition, disease severity and balance performance in individuals with COPD. In addition, balance performance in COPD participants with and without cognitive impairment was examined. Understanding the contributions of disease severity and cognition to balance may lead to an optimal clinical assessment and intervention in this population.

Materials and methods

Participants

Fifty participants with COPD were recruited from a local hospital in Chiang Mai. This sample size was based on the recommendation for the sufficient sample required for correlation analysis.[15] All participants were diagnosed by a physician according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria.[16] The GOLD criteria are considered by two aspects; a ratio of forced expiratory volume in one second and forced vital capacity (FEV_1/FVC<70%, and a classification of severity using the percentage predicted level of forced expiratory volume in one second (%predictedFEV_1) following a standard spirometer recommended by American Thoracic Society/ European Respiratory Society (ATS/ERS) 2005.[17] Other inclusion criteria included age 40 years and older, and walking independently. Participants were excluded if they had a previous history of neurological conditions, musculoskeletal conditions that could interfere with standing and walking, and impaired visual ability. Ethical approval was gained from the ethical review committee for research in humans according to the Declaration of Helsinki (AMSEC-61EX-009), and all eligible participants signed a written informed consent prior to participating in this study.

Baseline characteristic assessments

Baseline characteristic assessments including age, gender, Body Mass Index (BMI), smoking history, COPD onset, modified Medical Research Council (mMRC) dyspnea, and six-minute walk test (6MWT) were recorded. The mMRC dyspnea questionnaire consists of five-grade scales (0-4) describing the severity of participants' breathlessness associated with physical activity from low breathlessness (0) to almost complete incapacity (4). The 6MWT was performed following the methodology specified by the American Thoracic Society.[18] The participants were instructed to walk as far as possible along the 30-meter corridor during the 6-minute duration. During the test, they were allowed to rest at any time as needed and walk again when ready. Dyspnea, heart rate, and oxygen saturation were continuously monitored throughout the test and blood pressure was assessed before and after the test. The 6MWT was measured for two trials with 30-min rest between trials. The longest distance was recorded.

Balance assessment

The TUG (single task) was used to measure balance performance as it has been widely used to identify balance deficit and risk of falls in individuals with COPD.[3, 4] In addition, TUG dual-task was also included to increase test's sensitivity for identifying balance problem.[8, 9] The secondary cognitive task was chosen over the motor task as previous study demonstrated that it was more challenging than the motor task.[19] The TUG has been shown to be a simple and reliable test for assessing balance and risk of falls.[20-22] Participants were asked to perform the TUG under single- and dual-task conditions in a random order. For TUG with dual-task, participants were asked to do a naming task while performing TUG test. Specifically, they were instructed to say as many names from a given category as possible. Category such as animals, fruits, flowers, provinces was given to the participants prior to each testing trial. A practice trial was allowed prior to each test condition, followed by two testing trials. Average time used to complete each condition was recorded.[23] A rest period of 3 minutes was given between each test. Tests were administered by an independent assessor who was blinded to the participant's disease severity

and cognitive condition.

Cognitive assessment

Montreal Cognitive Assessment-Basic (MoCA-B) Thai version was administered to all participants by a trained assessor according to standard instruction. The assessor was blinded to the participants' disease severity and balance performance. MoCA-B is a 30-point test that evaluates six cognitive domains including visual perception, executive functioning, language, attention, memory, and orientation. A score of 1 point is added to participants who had less than 4 years of education. MoCA-B score lower than 25 points indicates cognitive impairment and the score of 25 points and greater indicates normal cognitive function.[25] MoCA-B (Copyright Z. Nasreddine, MD) is freely available for clinical use in Thai, English, Chinese, and French (www.mocatest.org, visit Basic section). MoCA-B Thai version has excellent sensitivity and specificity and high test-retest reliability and internal consistency.[25]

Measure of COPD severity

FEV_1, FVC, and %predictedFEV_1 values with post-bronchodilator were assessed using spirometer (HI-101, CHEST M.I., Inc, Japan). The testing protocol was conducted by an experienced, certified investigator following the instruction specified by the European Respiratory Society recommendations.[17] The classification of COPD severity using the %predictedFEV_1 value was defined as follows; mild stage (GOLD I) %predictedFEV_1 ≥80%, moderate stage (GOLD II) %predictedFEV_1≥50% and <80%, severe stage (GOLD III) %predictedFEV_1 ≥30% and <50%, and very severe stage (GOLD IV) %predictedFEV_1<30%.[16]

Statistical analyses

The statistical analyses were performed using SPSS software. Descriptive statistics were used to describe demographic data and outcome measures. Kolmogorov-Smirnov test was used to determine the assumption of normality. Pearson's correlation coefficient was used to determine the association between the time to complete TUG and %predictedFEV_1; and between the time to complete TUG and MoCA-B score. The correlation coefficient between 0.9 to 1.0 indicates very high correlation, 0.7 to 0.9 indicates high correlation, 0.5 to 0.7 indicates moderate correlation, 0.3 to 0.5 indicates low correlation, and 0.0 to 0.3 indicates negligible correlation.[26] Participants were further classified into either cognitively-intact (MoCA-B score ≥25 points) or cognitively-impaired (MoCA-B score <25 points) subgroups. Independent sample student's t-test was used to determine the differences of balance performance between the two cognitive subgroups. A significance level was set at 0.05 for all analyses.

Results

Demographics of participants

Study participants included 50 individuals with COPD (37 men, 13 women) aged between 54 and 85 years. Of the 50 participants, 11 (22%) had mild, 24 (48%) had moderate, and 15 (30%) had severe stage of COPD. The average MoCA-B score was 22.9±4.5 points with the range between 9 and 29 points. Demographic characteristics of the participants are presented in Table 1.

Table 1 Demographic characteristics of participants (n=50).

Variables	Values (mean±SD)
Age (years)	69.8±7.8
Gender (male, %)	37 (74)
Body Mass Index; BMI (kg/m^2)	19.9±3.8
Smoking history (pack-years)	13.0±18.6
mMRC dyspnea (median, IQR)	1(1)
FEV_1 (L)	1.3±0.5
FVC (L)	2.3±0.7
FEV_1/FVC (%)	55.9±9.7
Disease severity (n)	
GOLD stage I	11
GOLD stage II	24
GOLD stage III	15
PredictedFEV_1 (%)	64.3±22.5
COPD onset (years)	3.9±3.9
MoCA-B score (points)	22.9±4.5
6MWD (m)	347.1±96.3

The data are expressed as mean±standard deviation, otherwise as indicated.
Notes: *SD: standard deviation, %: percentage, kg: kilogram, m: meter, mMRC: modified Medical Research Council, IQR: Interquartile range, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, L: liter, GOLD: Global Initiative for Chronic Obstructive Lung Disease, n: number, MoCA-B: the Montreal Cognitive Assessment-Basic, 6MWD: six-minute walk distance*

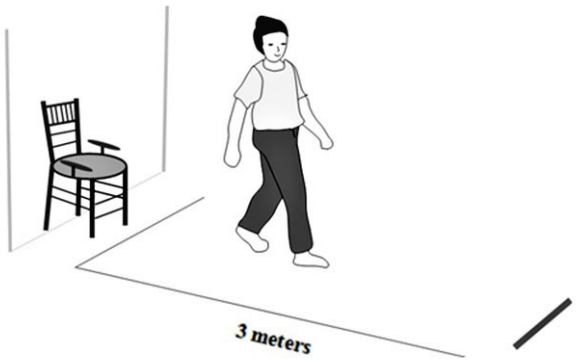

Figure 1 *The Timed Up and Go test*[24]

Balance performance and cognitive function, disease severity

Average time taken to accomplish TUG was 11.9±3.1 seconds for the single-task condition and 15.2±4.6 seconds for the dual-task condition. Pearson's correlation analysis revealed that the time taken to complete TUG for both single- and dual-task conditions was negatively correlated with MoCA-B score (p≤0.001) (Figure 2, 3). The correlation coefficients were comparable between both TUG conditions (TUG-single r =-0.47; TUG-dual r =-0.48), and indicated low relationship. There were no correlations between time to complete TUG in both conditions and %predictedFEV_1 (p>0.05).

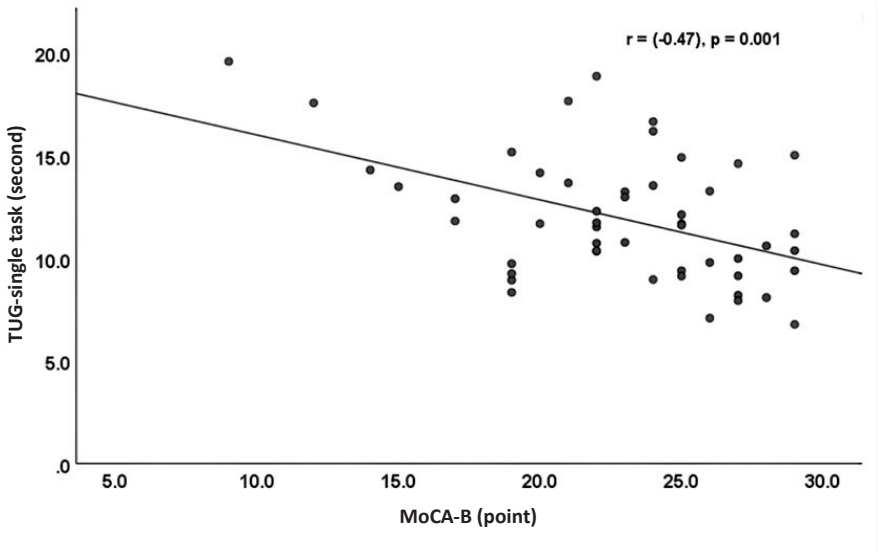

Figure 2 *The correlation of TUG-single task time and MoCA-B score*

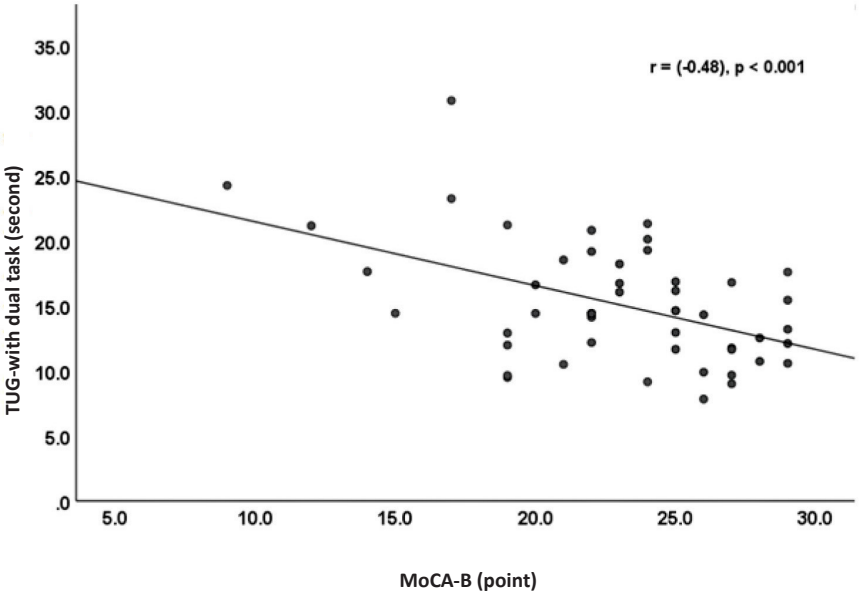

Figure 3 *The correlation of TUG-dual task time and MoCA-B score*

Comparison between cognitively-intact and cognitively-impaired COPD subgroups

Of the 50 participants, 29 participants were classified as having cognitive impairment based on MoCA-B cut-off score at 25 points.[25] Characteristics of the cognitively-intact and cognitively-impaired subgroups are shown in Table 2. There were no significant differences between groups for age, gender, BMI, dyspnea score, disease onset and exercise capacity (p>0.05).The cognitively-impaired group had significant lower of FEV_1, FEV_1/FVC and higher mean pack-years of smoking than the cognitively-intact group. The time to complete TUG-single and TUG-dual task was significantly longer for the cognitively-impaired group as compared to the cognitively-intact group (Table 3).

Table 2 Demographic characteristics of the cognitively-intact (n=21) and cognitively-impaired (n=29) subgroups.

Variables	Cognitively-intact COPD	Cognitively-impaired COPD	*p* value
Age (year)	67.5±7.5	71.4±7.8	0.08
Gender (male, %)	17 (81)	20 (69)	0.53
Body Mass Index; BMI (kg/m^2)	20.8±3.8	19.3±3.7	0.15
Smoking history (pack-years)	7.5±9.1	20.5±25.1	0.03
mMRC dyspnea (median, IQR)	1(1)	1(1)	1.00
FEV_1 (L)	1.4±0.5	1.1±0.4	0.03
FVC (L)	2.4±0.8	2.1±0.7	0.12
FEV_1/FVC (%)	58.9±9.1	53.7±9.8	0.06
PredictedFEV_1 (%)	71.8±24.0	58.9±20.1	0.05
COPD onset (year)	3.8±2.9	4.0±4.6	0.88
6MWD (m)	354.2±110.0	342.0±86.7	0.66

Notes: *%: percentage, kg: kilogram, m: meter, mMRC: modified Medical Research Council, IQR: Interquartile range, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, 6MWD: six-minute walk distance*

Table 3 TUG performance between the cognitively-intact (n=21) and cognitively-impaired (n=29) subgroups.

Variables	Cognitively-intact COPD	Cognitively-impaired COPD	Mean difference	95% CI	*p* value
TUG time (s)	10.5±2.5	13.0±3.1	2.5	-4.1,-0.9	0.003
TUG with dual task time (s)	12.9±2.8	16.8±5.0	3.9	-6.2,-1.7	0.001

Notes: *s: second, CI: confidence interval*

Discussion

The main findings of this study demonstrated that TUG performance, both single- and dual-tasks, of individuals with COPD were significantly correlated with MoCA-B score but not %predictedFEV_1. In addition, TUG performance was poorer in COPD individuals with cognitive impairment compared to those without cognitive impairment.

Balance control requires complex integration of multiple sensorimotor and cognitive processes.[27] The pertinent role of cognition in balance control has been revealed by several studies that demonstrated balance impairment in individuals with cognitive impairment such as mild cognitive impairment and Alzheimer's disease.[28, 29] The present study demonstrated negative correlation between MoCA-B score and time to complete TUG test. Lower MoCA-B score was correlated with longer time to complete TUG. This finding is in agreement with a previous study that reported a significantly negative correlation between Mini-Mental State Examination (MMSE) score and static posturography path length in elderly people (r=-0.25).[30] The correlation coefficient in both previous studies[29,30] and this study was, however, relatively low which might be explained partly by the use of global cognitive function tests (i.e. MoCA-B, MMSE). It has been suggested that balance control was related to some more than other cognitive domains.[29] Tangen *et al* [29] found that Balance Evaluation System Test (BESTest) score was significantly correlated with Trail Making test-part B (TMT-B) score but not with TMT-part A, clock drawing, word-list learning, verbal fluency, and MMSE scores. The authors concluded that balance control relies more on executive function than other cognitive domains. However, it remains unclear which cognitive domain is mostly correlated with TUG performance. Future study should examine the influence of specific cognitive functions on TUG performance.

The findings of comparable correlation coefficient between the single (r=-0.47) and dual-task (r=-0.48) conditions suggested that adding a cognitive task did not strengthen the relationship between balance and cognitive performance. However, the dual-task condition appeared to make the TUG test more challenging as reflected by an increase in the time to complete TUG under this condition in both cognitively-intact COPD (TUG single=10.5 seconds, TUG dual=12.9 seconds) and cognitively-impaired COPD (TUG single=13.0 seconds, TUG dual=16.8 seconds). This finding was supported by several studies that demonstrated significant increase in time taken to complete TUG under dual-task compared to single task conditions.[8, 23]

In the present study, there was no correlation between TUG performance and disease severity which was in accordance with findings from previous studies.[2, 31] de Castro *et al* [31] found no correlation between balance and pulmonary function. In addition, results from subgroup analyses based on the COPD severity demonstrated that performance on both static and functional balance, as assessed by one-legged

stance and TUG, were comparable across these subgroups.[31] Possible explanation for this finding is that TUG performance may be related to factors such as exercise capacity and lower limb muscle strength rather than disease severity.[2, 31] Jacome *et al*[2] also found that body mass index, number of medications, restriction in recreational activities, and depression were the multivariate predictors of balance impairment as measured by TUG.

The results derived from subgroup analysis demonstrated that the time taken to perform TUG in both conditions was significantly longer for the COPD with cognitive impairment than non-cognitive impairment subgroups. This result was in line with a recent systematic review and meta-analysis which demonstrated adverse effect of MCI on gait and balance.[28] Using TUG cut-off times for COPD at 11.2 seconds as recommended by Mesquita *et al*[32], the present finding indicated that the COPD with cognitive impairment subgroup were at risk of falls.[32] These findings suggested that cognitive impairment has negative impact on balance and consequently place individuals with COPD at risk of falls. A higher disease severity observed in the cognitive impairment subgroup was in accordance with previous systematic review which indicated significant link between disease severity and cognitive impairment in this population.[33]

Certain limitations must be considered when interpreting the results of this study. Given that all stages of disease severity were not included and the sample size was small, the generalizability of our results to the COPD population is limited. In addition, as this study was a cross-sectional design, the causal relationship of the study outcomes could not be inferred. In future studies, a longitudinal design with large sample size that includes all COPD severity is warranted. Furthermore, the role of specific cognitive domains on TUG performance should be investigated.

Conclusion

The present study demonstrated that balance performance was significantly correlated with cognitive performance but not COPD severity. Cognitive impairment adversely affected balance ability and put individuals with COPD at risk of falls. These findings confirmed the role of cognition in balance control. Thus, cognitive function should be included as part of a routine assessment in individuals with COPD and fall risk assessment should particularly be administered to COPD individuals who have cognitive impairment.

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