Cognitive Impairment and its Effect on Chronic Obstructive Pulmonary Disease: An Underestimated Phenomenon

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Abstract

Background: To assess the ability of the Rowland Universal Dementia Assessment Scale (RUDAS) to predict inhaler technique and determine the prevalence of cognitive impairment in chronic obstructive pulmonary disease (COPD). Patients and Methods: This cross-sectional study included 98 participants, and we recorded age, education, locality, occupation, COPD stage, comorbidities, duration of inhaler use, and smoking history. Inhaler technique was assessed using an internationally accepted schedule (nine steps). RUDAS, a multicultural cognitive assessment scale, was used to assess cognitive function. Results: The study included 92 males and 6 females with the mean age of 63.9 years. At a cutoff of 24, RUDAS had 93.6% sensitivity and 88.2% specificity in screening incorrect inhaler technique. Those having a RUDAS score <24 were 272 times more likely to perform incorrect inhaler technique. On comparison of incorrect and correct inhaler technique groups on various parameters in univariate analysis, it was found that the groups were significantly different in terms of education, locality, occupation, COPD stage, comorbidities, and smoking history. However, in logistic regression, only RUDAS score <24 was found to be a predictor of incorrect inhaler technique. At the original cutoff of 23, RUDAS screened 42.9% (n = 42) of the patients as having cognitive impairment. Conclusions: High prevalence of cognitive impairment among COPD patients and its untoward impact on inhaler technique is an important but underestimated clinical issue. RUDAS is an effective tool to predict incorrect inhaler technique and cognitive impairment in COPD.

Keywords: Chronic obstructive pulmonary disease, cognitive impairment, inhaler technique

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common respiratory condition, affecting 10%–15% of adults worldwide.[1] Its prevalence is on the rise, while the incidence in old age continues to grow.[2] It can lead to significant reduction in physical activity and psychological problems, all of which deteriorate the patient’s health-related quality of life.[3] COPD is a significant cause of mortality worldwide, amounting to 5% of deaths in the year 2015.[4] COPD can also be associated with various comorbidities such as reduced cardiac function, poor nutrition, anemia, loss of muscle mass, osteoporosis, cognitive impairment, clinical depression, anxiety, and gastrointestinal reflux disorder.[4]

Trouble with memory, new learning, and decision-making in day-to-day life are symptoms of cognitive impairment. COPD has been found to be associated with increased risk of cognitive impairment.[5] Cognitive impairment in COPD has been postulated due to a repeated exposure to hypoxia, leading to impaired functioning of enzymes required for neurotransmitter synthesis, eventually leading to neural dysfunction.[6,7] Recent research using functional magnetic resonance imaging has found that COPD individuals demonstrate loss of white matter as compared to controls. This may lead to disturbed gray matter activation and cognitive dysfunction.[8] Executive function, memory, and attention are involved in COPD-related cognitive dysfunction.[9] Impairments in executive functioning impair planning, goal setting, sequencing, execution, and monitoring. Previous research has found that cognitive impairment (drawing impairment) is a risk factor for mortality in severe COPD patients.[10]
Proper inhaler technique has been found to be a predictor of efficacy of therapy.\cite{11} However, the ability of patients to properly handle the device may get less importance among other things. This can lead to unnecessary escalation of treatment and hospitalization. An expert panel on inhaler adherence has recommended that improved knowledge of errors may help treating doctors in early identification and corrective measures.\cite{12} Hence, there is a need to identify clinical methods that can predict patient’s proficiency for inhaler technique. Previous research has found association between executive dysfunction and poor inhaler technique.\cite{13}

There are limited studies from rest of the world, done to predictability to learn inhaler technique using cognitive tests,\cite{14-16} and none from India, which was the primary aim of the study. The secondary aim of the study was to assess the prevalence of cognitive impairment in COPD patients.

**Patients and Methods**

A cross-sectional study was conducted among COPD patients coming to the outpatient department and/or admitted under the care of department of respiratory medicine at the institute and meeting inclusion and exclusion criteria, over a period of 6 months (from March 2018 to September 2018). Inclusion criteria were (a) adult patient of any age, gender; diagnosed with COPD using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (2017); (b) who have been clinically stable in the last 4 weeks prior to the study; and (c) who were on regular inhaler therapy since at least previous 2 months. Patients with a previous diagnosis of mental illness or cognitive dysfunction were excluded from the study.

Ethical approval was obtained from the Institutional Ethics Committee. Written informed consent was obtained from the participants before enrolment. A convenience sample of 100 patients with COPD was included.

The study data were collected under five headings: (1) Demography, (2) COPD status, (3) Comorbidities, (4) Evaluation of inhaler technique, and (5) Cognitive status. Demographic data included age, gender, locality, education, occupation, and smoking status. COPD status included duration of illness, severity of illness (using pulmonary function test report and GOLD criteria), medications that the participants were using, duration of inhaler use, number of times participant has been trained to use inhaler on earlier occasions by physician and other health-care workers, and oxygen saturation on the day of evaluation – was assessed using portable SpO2 monitor. Comorbidities based on clinical history (history of hypertension, diabetes, congestive heart failure, or any other). Inhaler technique assessed using an internationally accepted inhaler use schedule was used to assess the current inhaler technique of the participant [Box 1].\cite{17}

Cognitive function was assessed based on performance on the items of the Rowland Universal Dementia Assessment Scale (RUDAS).\cite{18} RUDAS was chosen because it is designed as a multicultural cognitive assessment scale which has set guidelines for use with a diverse set of population and guidelines for use in a different language than English. RUDAS is available in public domain and does not require permission to translate in another language. Gujarati version of RUDAS was developed using translation-back translation method. Face validity was assessed by agreement among the investigators and opinion of two psychiatrists, who were not part of the study, was taken. During pilot testing, it was found that three-dimensional wireframe used for assessment of Step 4, visuoconstructional drawing, was difficult for our patients. Hence, this was substituted with “Box in a Box” figure from the Hindi Mental Status Examination (HMSE).\cite{19} This figure was used because the original scoring could be applied to this figure.

**Statistical analysis**

Data were entered in Microsoft Excel, and codes were assigned to raw data. Data were analyzed using STATA version 14, StataCorp, Texas, USA and JAMOVI 0.9.1.6, www.jamovi.org. Descriptive statistics were calculated for demographic data, COPD profile, comorbidities, and inhaler technique. Ability to use inhaler was considered incorrect if any of the steps were done incorrectly [Box 1]. Receiver operating characteristic (ROC) curve and cutoff score for ability of RUDAS score in predicting incorrect inhaler technique was calculated. Demographics, disease, medication, comorbidity, and smoking-related factors associated with incorrect inhaler technique were explored using cross-tabulation, and Chi-square test was used to assess significance of difference. The threshold for significant difference in this study was 0.05. Variables were entered in the logistic regression model for incorrect inhaler technique: age, education category, rural/urban, occupation, COPD stage, any comorbidity, duration of inhaler use, smoker type, and RUDAS category (<24 and ≥24, based on ROC analysis). Prevalence of cognitive impairment in COPD patients was calculated using the original RUDAS
cutoff score of 23/30. Correlation of age with RUDAS score was calculated.

**RESULTS**

One-hundred patients were included in the study. Ninety-eight were included in the analysis (two patients, who were never trained by any health-care worker for inhaler use, were excluded). The study population included 92 males (93.9%) and 6 females (6.1%). Mean (standard deviation [SD]) age of the study population was 63.9 (9.3) years. Three-fourths (n = 74, 75.5%) were from rural areas. Fifty-seven percent (n = 56) had 7 or more years of education. Majority of the population (86.7%) represented semiskilled workers or laborers. Almost half (n = 50, 51%) were chronic smokers [Table 1].

More than 90% (n = 90) have moderate-to-severe COPD, according to the GOLD criteria. Forty patients (41.8%) had comorbid medical conditions. About 80% (n = 78) were on both oral medications and inhalers [Table 2].

Ninety-nine percent (n = 97) were using dry powder inhalers. Majority of the patients (98%) had been trained for inhaler use technique by respiratory physician, with a median of 5 explanations for the study population. More than three-fourth (n = 76, 77.6%) of the patients had never been explained the inhaler procedure by any other health-care worker. Forty-eight percent (n = 47) demonstrated correct method of inhaler use. Fifty-two percent (n = 53) made errors on sequence of inhaler use and 48% (n = 49) made critical step errors. On the nine steps of the inhaler technique, our study participants had a mean (SD) score of 7.8 (1.25) correct steps (n = 98).

Figure 1 shows the ROC curve for ability of RUDAS score in predicting incorrect inhaler technique. The area under the curve (AUC) was 0.922 (95% confidence interval [CI] [0.863, 0.982]). At a cutoff of 23.5/24, RUDAS had 93.6% sensitivity and 88.2% specificity in screening incorrect inhaler technique. At this cutoff, RUDAS has a positive likelihood ratio (LR) = 7.93 and negative LR = 0.072 for screening incorrect inhaler technique.

ROC curve for ability of RUDAS visuoconstructional task (draw box in bow) in predicting incorrect inhaler technique was also calculated (figure not shown). The score for this question was recoded into 0 = mistake in any of the tasks and 1 = able to do all tasks in question. The AUC was 0.615, and it had a 93.6% sensitivity and 29.4% specificity in screening incorrect inhaler technique.

On comparison of the incorrect and correct inhaler technique groups on various parameters in univariate analysis, it was found that the groups did not differ in terms of age or duration of inhaler use. However, they were significantly different in terms of education, locality, occupation, COPD stage, comorbidities, and history of smoking [Table 3].

The following variables were entered in the logistic regression model for incorrect inhaler technique: age, education category, rural/urban, occupation, COPD stage, any comorbidity, duration of inhaler use, smoker type, and RUDAS category (<24 and ≥ 24). Of these, only RUDAS score < 24 was found to be a predictor of incorrect inhaler technique [Table 4].

Baseline model could predict incorrect inhaler technique, 52% of the time (same as tossing a coin). Once the variables were entered in the model, omnibus test of model coefficients found significant improvement over the baseline model (P < 0.001). Nagelkerke $R^2$ (0.80) suggests that the entered model could explain 80% variation in the outcome. The model was a good fit for the data as the Hosmer and Lemeshow test, $P = 0.107$ (>0.05). The model could correctly predict incorrect inhaler technique 94% times. Those having a RUDAS score < 24 are 272 times more likely than those having a normal score to perform incorrect inhaler technique.

At the original cutoff of 23/30, RUDAS was screened 42.9% (n = 42) of the patients as having cognitive

| Variable | Characteristic | n (%) |
|----------|----------------|-------|
| Age      | Mean (SD)      | 63.9 (9.3) |
|          | Minimum-maximum| 45-90 |
| Gender   | Male           | 92 (93.9) |
|          | Female         | 6 (6.1) |
| Locality | Rural          | 74 (75.5) |
|          | Urban          | 24 (24.5) |
| Years of formal education | 0-6          | 42 (42.9) |
|          | 7 or more      | 56 (57.1) |
| Occupation | Skilled       | 5 (5.1) |
|          | Semi-skilled   | 41 (41.8) |
|          | Laborer        | 44 (44.9) |
|          | Homemaker      | 4 (4.1) |
|          | Unemployed     | 4 (4.1) |
| Smoker type | Chronic smoker | 50 (51) |
|          | Ex-smoker      | 26 (26.5) |
|          | Never smoker   | 22 (22.4) |

SD: Standard deviation
dysfunction and 57.1% (n = 56) as not having cognitive dysfunction. Correlation coefficient of RUDAS score with education was 0.639 (P < 0.001). Mean (SD) score of participants with RUDAS score <23 on the steps of inhaler technique (6.69 [0.75], n = 42) was significantly lower than mean (SD) of participants with RUDAS score >23 was (8.63 [0.84], n = 56, P ≤ 0.0001).

### DISCUSSION

COPD is considered a respiratory disease, but it can cause disabling extrapulmonary effects including cognitive impairment. Cognitive impairment can hamper the patient’s proficiency to handle the inhaler device. We found that at a cutoff of 24/30 RUDAS had 93.6% sensitivity and 88.2% specificity in predicting incorrect inhaler technique. A study by Gray et al. to predict inhaler technique by using Mini-Mental Status Examination (MMSE) found that a score <24 had 54.8% sensitivity and 80% specificity (odds ratio, 3.66; 95% CI, 1.07–12.4) in predicting incorrect inhaler technique.[14] Allen et al. used four cognitive tests to predict proficiency of metered-dose inhaler use, MMSE was one of them, which had a sensitivity of 57% and specificity of 76%.[15]

A pilot study done to compare MMSE and HMSE reported that both tools are variable and weak to classify cognitive impairment.[20] These preliminary results suggest that in our population where MMSE has limitations of use due to language and education bias, RUDAS has better sensitivity and specificity in predicting the ability to use inhaler. RUDAS is simpler, less language, and educationally biased tool that can be used for screening patients who may have difficulties in learning inhaler use.

In our study, RUDAS visuoconstructional task (draw box in a box) had 93% sensitivity and 29% specificity in predicting incorrect inhaler technique. Quite similarly, Board and Allen had done a study using overlapping pentagons and reported that those who were doing poorly in the drawing test were unable to

| Variable | Characteristic | Incorrect inhaler technique (n=51) | Correct inhaler technique (n=47) | P |
|----------|----------------|-----------------------------------|---------------------------------|---|
| Age (years) | Mean (SD) | 62.8 (8.1) | 65.0 (10.5) | 0.25 |
| Education (years) | 0-6 | 30 (51.8) | 12 (25.5) | 0.001 |
| | 7 or more | 21 (41.2) | 35 (74.5) | 0.022 |
| Locality | Rural | 45 (88.2) | 29 (61.7) | 0.001 |
| | Urban | 6 (11.8) | 18 (38.3) | 0.001 |
| Occupation | Skilled | 1 (2.0) | 4 (8.5) | 0.007 |
| | Semi-skilled | 14 (27.4) | 27 (57.4) | 0.001 |
| | Laborer | 31 (60.8) | 13 (27.7) | 0.001 |
| | Homemaker | 3 (5.9) | 1 (2.1) | 0.001 |
| | Unemployed | 2 (3.9) | 2 (4.3) | 0.001 |
| COPD stage | Mild | 6 (11.8) | 2 (4.2) | 0.012 |
| | Moderate | 28 (54.9) | 39 (83.0) | 0.001 |
| | Severe | 17 (33.3) | 6 (12.8) | 0.001 |
| Any comorbidity | Yes | 22 (43.1) | 36 (76.6) | 0.001 |
| | No | 29 (56.9) | 11 (23.4) | 0.001 |
| Duration of inhaler use (years) | Mean (SD) | 2.39 (1.28) | 2.87 (1.40) | 0.07 |
| Smoker type | Chronic smoker | 36 (70.6) | 14 (29.8) | <0.001 |
| | Ex-smoker | 13 (25.5) | 13 (27.7) | <0.001 |
| | Never smoker | 2 (3.9) | 20 (42.5) | <0.001 |
| RUDAS score | <24 | 45 (88.2) | 3 (6.4) | <0.001 |
| | 24-30 | 6 (11.8) | 44 (93.6) | <0.001 |

SD: Standard deviation, COPD: Chronic obstructive pulmonary disease, RUDAS: Rowland Universal Dementia Assessment Scale

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**Table 2: Chronic obstructive pulmonary disease profile of the study population (n=98)**

| Variable | Characteristic | n (%) |
|----------|----------------|-------|
| COPD stage | Mild | 8 (8.2) |
| | Moderate | 67 (68.4) |
| | Severe | 23 (23.5) |
| Comorbidities* | Yes | 40 (40.8) |
| | No | 58 (59.2) |
| Current medications | Only oral | 1 (1)** |
| | Inhaled | 19 (19.4) |
| | Both oral and inhaled | 78 (79.6) |
| Type of medications | SABA | 97 (99) |
| | SAM | 40 (40.8) |
| | LABA | 92 (93.9) |
| | LAMA | 9 (9.2) |
| | ICS | 92 (93.9) |
| | Oral bronchodilator | 78 (79.6) |

*Hypertension 38 (38.8), diabetes mellitus 15 (15.3), Other 1 (1), **With past history of inhaler use. COPD: Chronic obstructive pulmonary disease, SABA: Short Acting Beta-2 Agonist, SAM: Short Acting Muscarinic Antagonist, LABA: Long Acting Beta-2 Agonist, LAMA: Long Acting Muscarinic Antagonist, ICS: Inhaled Corticosteroid

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**Table 3: Comparison of the incorrect and correct inhaler technique groups on various parameters (n=98)**

| Variable | Characteristic | Incorrect inhaler technique (n=51) | Correct inhaler technique (n=47) | P |
|----------|----------------|-----------------------------------|---------------------------------|---|
| Age (years) | Mean (SD) | 62.8 (8.1) | 65.0 (10.5) | 0.25 |
| Education (years) | 0-6 | 30 (51.8) | 12 (25.5) | 0.001 |
| | 7 or more | 21 (41.2) | 35 (74.5) | 0.022 |
| Locality | Rural | 45 (88.2) | 29 (61.7) | 0.001 |
| | Urban | 6 (11.8) | 18 (38.3) | 0.001 |
| Occupation | Skilled | 1 (2.0) | 4 (8.5) | 0.007 |
| | Semi-skilled | 14 (27.4) | 27 (57.4) | 0.001 |
| | Laborer | 31 (60.8) | 13 (27.7) | 0.001 |
| | Homemaker | 3 (5.9) | 1 (2.1) | 0.001 |
| | Unemployed | 2 (3.9) | 2 (4.3) | 0.001 |
| COPD stage | Mild | 6 (11.8) | 2 (4.2) | 0.012 |
| | Moderate | 28 (54.9) | 39 (83.0) | 0.001 |
| | Severe | 17 (33.3) | 6 (12.8) | 0.001 |
| Any comorbidity | Yes | 22 (43.1) | 36 (76.6) | 0.001 |
| | No | 29 (56.9) | 11 (23.4) | 0.001 |
| Duration of inhaler use (years) | Mean (SD) | 2.39 (1.28) | 2.87 (1.40) | 0.07 |
| Smoker type | Chronic smoker | 36 (70.6) | 14 (29.8) | <0.001 |
| | Ex-smoker | 13 (25.5) | 13 (27.7) | <0.001 |
| | Never smoker | 2 (3.9) | 20 (42.5) | <0.001 |
| RUDAS score | <24 | 45 (88.2) | 3 (6.4) | <0.001 |
| | 24-30 | 6 (11.8) | 44 (93.6) | <0.001 |

SD: Standard deviation, COPD: Chronic obstructive pulmonary disease, RUDAS: Rowland Universal Dementia Assessment Scale
learn inhaler use (93% specificity). While Allen et al. found a 75% sensitivity and 79% specificity in predicting incorrect inhaler technique using intersecting pentagons. They also used a clock-drawing task (CLOX) as a measure of executive function in predicting incorrect inhaler technique. They found that CLOX1 score <10 had 83% sensitivity and 57% specificity, whereas CLOX2 score <12 had 58% sensitivity and 64% specificity in predicting incorrect inhaler technique. Hence, in settings when the clinician is pressed for time, the RUDAS drawing task can yield good sensitivity in predicting ability to use inhaler. Furthermore, it can be given to the patient to perform while they are in the waiting area.

In our study, representing mainly participants with moderate-to-severe COPD, 42% screened positive for cognitive impairment at the original cutoff of 23/30 for RUDAS. In an Indian study done by Gupta et al., to assess cognitive impairment in nonhypoxemic COPD patients using MMSE and P300 test, they found that 10 out of their 40 (25%) patients demonstrated prolonged P300 latency and 27 out of 40 (67.5%) patients had MMSE scores lower than 99th percentile healthy volunteers.

High prevalence of cognitive impairment in our study population raises awareness about the need for addressing this problem in our clinical settings. This is particularly necessary as cognitive impairment can lead to trouble in remembering, learning new things, concentrating, or making decision. This can make handling money and medications (part of the instrumental activities of daily living [IADL]) difficult. This is corroborated by research which has shown that increase in cognitive impairment over the course of illness is associated with reduction in IADL scores.

Andrianopoulos et al. have recommended that health-care professionals must be mindful of cognitive impairment in their COPD patients and when present should be a trigger for better rehabilitation. Findings of above and our study suggest that regular screening of cognition must be done in COPD patients.

Strengths of the study
Investigators were mindful on developing inclusion criteria such that finally, 98% participants had been trained for inhaler use technique by respiratory physician, with a median of five explanations per participant. Despite this level of training, 48% of the patients had incorrect inhaler technique on evaluation. No previous work on these lines has been done in Indian settings.

Cross-sectional study, small sample size, male bias, and small representation of patients having mild illness are some of the limitations of this study. For screening of cognitive dysfunction RUDAS demonstrated education effects. Further research is required with education neutral or less educationally biased locally developed tools in a larger sample size on drug-naïve patients, who are serially followed up to evaluate natural course of ability to use inhaler.

Conclusions
High prevalence of cognitive impairment among COPD patients and its untoward impact on inhaler technique is an important but underestimated clinical issue. RUDAS is an effective tool to predict incorrect inhaler technique and cognitive impairment in COPD.

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