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## Assessment of Breathlessness in Lung Cancer: Psychometric Properties of the Dyspnoea-12 Questionnaire

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3 **Title Page**4 **Assessment of Breathlessness in Lung Cancer: Psychometric Properties of the**  
5 **Dyspnoea-12 Questionnaire**6  
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## 33 **Assessment of Breathlessness in Lung Cancer: Psychometric Properties of** 34 **the Dyspnoea-12 Questionnaire**

### 35 **Abstract**

36 **Content:** The Dyspnoea-12 (D-12) is a well validated instrument in respiratory illnesses for  
37 breathlessness assessment, but its psychometric properties have not been tested in lung cancer.

38 **Objectives:** To demonstrate the psychometric properties of the D-12 in lung cancer patients.

39 **Methods:** Baseline data from a lung cancer feasibility trial were adopted for this analysis. D-12 and a  
40 series of patient-reported tools including five Numeric Rating Scales (NRS), the Hospital Anxiety and  
41 Depression Scale (HADS) and the Lung Cancer Symptom Scale (LCSS) were employed for the  
42 psychometric assessment. Spearman's correlation coefficients ( $r_s$ ) were used to estimate the  
43 convergent validity of the D-12 with the NRS, HADS and LCSS. Exploratory factor analysis was  
44 performed to examine construct validity. Reliability was tested by Cronbach's alpha and item-to-total  
45 correlations. D-12 score difference between patients with or without anxiety, depression and COPD  
46 was explored to identify its discriminate performance.

47 **Results:** One hundred and one lung cancer patients were included. There were significantly positive  
48 correlations between the D-12 and the HADS, LCSS, and NRS scales measuring the breathlessness  
49 severity and its associated affective distress. Factor analysis clearly identified two components  
50 (physical and emotional) of the D-12. Cronbach's alpha for D-12 total, physical and emotional  
51 subscales was 0.95, 0.92 and 0.94, respectively. Patients with anxiety or depression demonstrated  
52 significantly higher D-12 scores than those without it, and patients with COPD reported significantly  
53 more severe breathlessness than those without COPD.

54 **Conclusion:** The D-12 is a valid and reliable self-reported questionnaire for use in breathlessness  
55 assessment in lung cancer patients.

56

### 57 **Key Words**

58 Breathlessness; Lung cancer; Scale; Psychometrics; Validity; Reliability

59

### 60 **Running title**

61 Validation of the Dyspnoea-12 in Lung Cancer

62 **Accepted for publication: August 4, 2016.**

## 63 **Introduction**

64 Breathlessness is defined as “a subjective experience of breathing discomfort that consists of  
65 qualitatively distinct sensations that vary in intensity” [1]. It is one of the most distressing symptoms  
66 frequently identified in lung cancer [2-5]. Evidence supports breathlessness as a multidimensional  
67 experience, as the presence of breathlessness is associated with physical and emotional distress such  
68 as fatigue, anxiety, depression, and deterioration of quality of life (QoL) [2, 5, 6]. As breathlessness is  
69 a subjective symptom involving both physical and psychological factors, its measurement should  
70 be multidimensional using patient-reported approaches that encompass its different dimensions [1,  
71 7].

72 There is a plethora of instruments for assessing breathlessness, although most of them have been  
73 validated for chronic obstructive pulmonary disease (COPD) [8]. Commonest used unidimensional  
74 tools for breathlessness assessment include the modified Borg scale, visual analogue scale (VAS) and  
75 numerical rating scale (NRS) [8, 9]. Although these tools are easy to complete, the use of different  
76 endpoints makes it difficult to do comparisons between studies [8], and their unidimensional nature  
77 requires the use of multiple instruments to obtain a full understanding of breathlessness. The  
78 Medical Research Council (MRC) dyspnoea scale is also a popular tool for grading breathlessness  
79 [8]. However, it is only activity-specific and it is weak in its association with patients’ physiological  
80 and functional distress, which make it impossible to use for the multidimensional assessment of  
81 breathlessness [8, 10].

82 Multidimensional instruments for breathlessness assessment have been introduced, such as the  
83 Cancer Dyspnoea Scale (CDS) [11-13]. But the CDS only includes the anxiety as patients’  
84 psychological distress and the evidence in terms of its responsiveness and minimal clinically  
85 important difference (MCID) is lacking [11-14]. The Chronic Respiratory Questionnaire (CRQ) is a  
86 good candidate for breathlessness assessment [14]. It has been well validated in chronic respiratory  
87 diseases such as COPD and interstitial lung disease (ILD) [14], and the psychometric properties of its  
88 short form have also been preliminarily identified in lung cancer [15]. However, the patient may  
89 take a relatively long time to complete the entire CRQ, and small changes in breathlessness may not  
90 be captured by repeated administration of the CRQ [16, 17]. Another tool named Breathlessness  
91 Assessment Guide has also been developed for lung cancer without any psychometric testing [18,  
92 19]. There is a shortage of instruments that could be used for measuring breathlessness among  
93 different advanced diseases [8].

94 The Dyspnoea-12 (D-12) is a convenient patient-reported scale for measuring the severity of  
95 breathlessness [20]. Breathlessness is quantified by using 12 descriptors to cover both its  
96 physical and psychological dimensions [20]. The D-12 has established its validity and reliability in  
97 COPD [20], asthma [21], ILD [22] and pulmonary hypertension [23], but its psychometric properties  
98 have not yet been assessed in lung cancer. Therefore, the aim of this study was to determine the  
99 validity and reliability of the D-12 in lung cancer, by using data from a recent lung cancer feasibility  
100 randomised controlled trial (RCT) [24].

## 101 **Materials and Methods**

102 Research ethical approval was granted to this study, and research governance approval was also  
103 received from the study hospitals. All participants provided written informed consent.

## 104 **Overview of the Feasibility Trial**

105 This was a multi-centre feasibility RCT conducted in the UK [24]. It aimed to feasibility test a non-  
106 pharmacological intervention for managing the lung cancer respiratory distress symptom cluster  
107 (breathlessness-cough-fatigue). The intervention consisted of a couple of self-management  
108 approaches such as the techniques for breathing control, cough easing and self-acupressure [24]. A  
109 total of 107 lung cancer patients joined the study and 101 were included in the analysis. Participants  
110 completed self-reported outcome measures including a range of scales to assess symptoms,  
111 psychological distress and QoL [24]. In the current study, only baseline data were used for analysis.

## 112 **Study Instruments**

113 The most pertinent outcome measures for examining the D-12 psychometric properties were  
114 included in this analysis.

### 115 ***-Dyspnoea-12 Questionnaire (D-12)***

116 The D-12 uses 12 items to generate a global assessment of the severity of breathlessness [20].  
117 Each item is rated on a 4-point Likert scale from 0 (none) to 3 (severe), and the total scores range  
118 from 0 to 36 with a higher score indicating more severe dyspnoea [21-23]. Items 1 to 7 are  
119 summed up to create the physical component score, and items 8 to 12 are used for calculating the  
120 emotional component score [21, 23]. MCID of the D-12 has been determined in the feasibility trial  
121 using anchor-based and distribution-based methods, with a value of 3 units [24].

### 122 ***-NRS Breathlessness Scales***

123 Five 0-10-point NRS scales were adopted to measure the average and worst breathlessness  
124 experienced during the past 24 hours (higher scores=worse conditions), breathlessness-related  
125 unpleasantness and distress (higher scores=worse conditions), and patients' ability to cope with  
126 breathlessness (higher scores=better conditions) [24-26]. The NRS scales were used to explore the  
127 associations with the D-12 total and component scores.

### 128 ***-Hospital Anxiety and Depression Scale (HADS)***

129 The HADS is a 14-item self-reported instrument for determining the general state of psychological  
130 distress, with seven items each assessing anxiety and depression respectively [27, 28]. Each item is  
131 rated from 0 to 3, thus the scores for either anxiety or depression scale range from 0 to 21 (higher  
132 scores=more severe outcomes) [27, 28]. For particular statistical purpose, a HADS anxiety score  
133 (HADS-A) of 8.0 or above was suggested as the presence of anxiety while a HADS depression score  
134 (HADS-D) of 8.0 or above was indicated as the presence of depression [28, 29]. The HADS was  
135 employed to explore the association with the D-12 as they both contain an emotional content for  
136 measuring psychological distress.

### 137 ***-Lung Cancer Symptom Scale (LCSS)***

138 The LCSS is a QoL assessment tool with well documented psychometric properties [30, 31]. The LCSS  
139 patient-reported scale consists of nine items with six assessing prominent symptoms related to lung  
140 cancer and another three evaluating patients' "symptomatic distress", "activity status" and "overall  
141 QoL" [30]. All items use the 0-100 VAS scale (higher scores=worse outcomes) and the total score is  
142 computed as the mean of all the nine items [32]. The LCSS was used to explore its correlations with  
143 the D-12 as QoL in lung cancer has been proved to be negatively associated with dyspnoea [5].

## 144 **Psychometric Assessment**

### 145 ***-Reliability and Validity***

146 Internal consistency reliability for the D-12 was examined and the item-to-total correlations were  
147 adopted to explore the relationships between one single D-12 item score and the total D-12 score  
148 without that item [33]. Validity was examined by convergent validity and construct validity.  
149 Convergent validity is estimated by examining “whether the measured variables correlate with other  
150 measures of the same concept” [34]. Associations between the D-12 and the NRS, HADS and LCSS  
151 were explored to identify the D-12 convergent validity. Exploratory factor analysis (EFA) was  
152 applied to estimate the D-12 construct validity.

### 153 **-Acceptability, Floor and Ceiling Effects, Invariance and Discriminate Performance**

154 Acceptability of the D-12 was estimated by calculating the percentage of missing value across all the  
155 D-12 items. Percentages of the subjects who had the lowest and highest possible D-12 total score  
156 were computed respectively to estimate the floor and ceiling effects of the D-12. Invariance of the D-  
157 12 was tested for age and gender factors. Discriminate performance analyses were considered for  
158 subjects with or without anxiety, depression and COPD.

### 159 **Statistical Analysis**

160 The IBM SPSS Statistics for Windows version 22.0 (IBM Corp, Armonk, NY, USA) was adopted for  
161 data analysis with the statistical significance setting as  $P<0.05$ . Descriptive statistics were presented  
162 to summarise patients’ demographic data, acceptability, and the floor and ceiling effects of the D-12.  
163 Spearman’s correlation coefficients ( $r_s$ ) were adopted for exploring the associations between the D-  
164 12 and the NRS, HADS and LCSS, as most of the instrument scores in our sample violated the  
165 assumption of normal distribution. Principal component analysis (PCA) with a varimax rotation  
166 (eigenvalues  $>1$ ) was used for the EFA. Items that loaded  $>0.6$  were retrieved for a potential factor.

167 Independent-samples t-test or Mann-Whitney U test (as determined by the normality test) was  
168 adopted to estimate the D-12 score difference in different subgroups (e.g. anxious vs. not anxious,  
169 and COPD vs. non-COPD). Age difference was analysed by exploring the association ( $r_s$ ) between the  
170 D-12 and patients’ age. Internal consistency was estimated by Cronbach’s alpha, and an alpha score  
171 of 0.8 or above is determined as very good for an instrument [35]. An item-to-total correlation is  
172 viewed as adequate once the value reaches 0.4 [36].

## 173 **Results**

### 174 **Patients’ Demographic and Clinical Data**

175 One hundred and one participants were included. The majority of the patients were aged over 60  
176 years old and had dyspnoea. Around one third of them presented anxiety or depression (**Table 1**).

### 177 **D-12 Descriptive Analysis**

178 The mean score for D-12 total was 17.8 (SD=9.4), and it was 11.0 (SD=5.3) and 6.6 (SD=4.8) for D-12  
179 physical and D-12 emotional subscale, respectively (**Figure 1**). Missing values within the D-12 were  
180 identified in no more than four subjects for each item across items 1 to 8. No missing data were  
181 detected for items 9 to 12. Proportions of the patients with the lowest (0) and possibly highest score  
182 (as of 35 in this sample) of the D-12 total were 4.0% (4/101) and 1.0% (1/101), respectively.

### 183 **D-12 Convergent Validity**

184 D-12 scores were strongly and positively correlated with HADS and LCSS scores (all at  $P<0.001$ ). The  
185 highest  $r_s$  was identified between D-12 emotional subscale and HADS anxiety subscale ( $r_s=0.71$ ,  
186  $P<0.001$ ). Significantly positive correlations can be found between D-12 and NRS “average” and  
187 “worst” breathlessness, and “distress” and “unpleasantness” associated with breathlessness ( $r_s$

188 ranged from 0.48 to 0.64, all at  $P < 0.001$ ). Slightly negative (but insignificant) correlations were  
189 shown between D-12 and NRS “ability to cope with breathlessness” ( $P > 0.05$ ) (Table 2).

### 190 **D-12 Construct Validity**

191 There were two well-defined factors with items 1 to 7 clustering around the first factor (coefficients  
192 ranged from 0.68 to 0.81, representing the physical dimension of breathlessness) and items 8 to 12  
193 gathering around the second factor (coefficients ranged from 0.78 to 0.87, indicating the emotional  
194 dimension of breathlessness) (Table 3).

### 195 **D-12 Reliability**

196 Internal consistency of the entire D-12 questionnaire was already reported in the feasibility study  
197 paper, with the Cronbach’s alpha of 0.95 [24]. Internal consistency for the D-12 physical and  
198 emotional subscales was also excellent, with Cronbach’s alpha being 0.92 and 0.94, respectively.  
199 Adequate item-to-total correlations of the D-12 were identified, with the coefficients ranging from  
200 0.59 to 0.84 (mean 0.8).

### 201 **D-12 Invariance and Discriminate Performance**

202 There was no difference in D-12 scores between male and female patients (all at  $P > 0.05$ ), and  
203 Spearman’s correlation also showed no association between D-12 and age ( $r_s$  ranged from -0.15 to -  
204 0.12, all at  $P > 0.05$ ). Patients with anxiety or depression presented significantly higher D-12 scores  
205 than those without anxiety or depression (all at  $P < 0.001$ ) (Table 4). Similarly, patients with COPD  
206 also had significantly higher D-12 scores than non-COPD patients (all at  $P < 0.05$ , Table 5).

### 207 **Discussion**

208 The D-12 is a short scale confirming earlier reports in non-cancer populations that has minimal  
209 missing data [23]. Acceptability of the D-12 was documented, as missing values across items and the  
210 floor and ceiling effects were minimal in the lung cancer sample. Given the good completion rate of  
211 the D-12 and its ability to gain an overall score that incorporates multidimensional aspects of  
212 dyspnoea severity, the clinical utility of the D-12 seems promising.

213 Convergent validity of the D-12 was adequate. The significantly positive associations between the  
214 D-12 and the NRS scales indicated the possibility of using one single instrument instead of multiple  
215 tools to measure the overall severity of breathlessness. There was a negative (but insignificant)  
216 correlation between the D-12 and patients’ coping ability, which indicated that severe dyspnoea  
217 might impair the patients’ ability to cope with the symptom. However, it is also suggested that the  
218 distress induced by the symptoms emotional component might, in turn, motivate patients’ behaviour  
219 [21]. The potentially bidirectional function of psychological distress might partially contribute to the  
220 above insignificant correlation. As coping ability is a complex construct which is almost impossible to  
221 capture in a single item scale, its relationship with dyspnoea is worthy of further exploration.

222 The D-12 was strongly correlated with anxiety and depression, as both the HADS and D-12 possess  
223 the psychological construct that measures patients’ emotional status. Theoretically, D-12 emotional  
224 subscale would be expected to correlate more strongly with the HADS than the D-12 physical  
225 subscale, and this assumption was precisely captured in our findings. Similar to our previous findings  
226 [21-23], correlations between D-12 and HADS were only moderate. This suggested the difference of  
227 the focus of emotional distress between D-12 and HADS, with the former capturing the emotional  
228 status related to dyspnoea and the latter focusing more on the general status of emotional problems  
229 [23].

230 Breathlessness is a negative predictor of QoL in lung cancer [2, 5, 37], and this was sensitively  
231 captured by the D-12 as significant correlations were shown between D-12 and LCSS. Factor analysis  
232 supported very good construct validity of the D-12, which was highly consistent with the factor  
233 analysis result during the development stage of the D-12 [20].

234 It is not surprising that no gender and age difference was detected across D-12 scores, as age and  
235 gender have been reported not to be related to dyspnoea in lung cancer [6]. Also, during the D-12  
236 development stage, items with gender or age bias had already been abandoned [20, 22]. Patients  
237 with anxiety or depression experienced more severe dyspnoea than those without such affective  
238 distress, as expected, because emotional problems such as anxiety and depression have been noted to  
239 be closely associated with breathlessness distress in lung cancer [6, 38, 39].

240 Breathlessness is one of the leading symptoms in COPD [40, 41]. COPD patients tend to experience  
241 similar or more severe dyspnoea and impaired QoL than that in lung cancer patients at a  
242 comparable advanced disease stage [42-44]. Lung cancer patients with COPD are expected to  
243 experience more severe dyspnoea than those without COPD, and this was accurately captured by  
244 the D-12 as patients with COPD had significantly higher D-12 scores than non-COPD patients.

245 The study has some limitations. Sample size estimation in the feasibility trial was not powered for  
246 the purpose of estimating psychometric properties. The D-12 scores in the control group subjects  
247 were not appropriate for estimating test-retest reliability because there was not a suitable anchor  
248 from the outcome measures that can be used to ensure patients' stability over time. D-12 divergent  
249 validity was also not performed due to the absence of available data. Despite these limitations, our  
250 study demonstrated that the D-12 is a valid and reliable assessment for breathlessness in lung  
251 cancer. Given its MCID was also identified [24], the D-12 can be a good option for use in future lung  
252 cancer trials to measure patients' breathlessness severity. Also, psychometric properties of the D-  
253 12 in lung cancer are consistent with previous validation studies in other respiratory diseases  
254 [20-23], which indicates its promising role for measuring breathlessness in a wide range of  
255 conditions.

## 256 **Conclusion**

257 D-12 is a valid and reliable patient-reported instrument for measuring breathlessness in patients  
258 with lung cancer. Future lung cancer studies are encouraged to adopt the D-12 as one of the outcome  
259 measures for breathlessness assessment.

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## 362 TABLES

363 Table 1 Demographic and clinical characteristics of the study sample (N=101)

Demographic and clinical characteristics		Number (%)
Age (year)	80-99	7 (6.9)
	60-79	80 (79.2)
	40-59	13 (12.9)
	20-39	1 (1.0)
	Mean (SD)	67.7±9.6
Gender	Female	54 (53.5)
	Male	47 (46.5)
Employment Status	Retired	59 (58.4)
	Retired for health reasons	25 (24.8)
	In paid employment	7 (6.9)
	Self-employed	2 (2.0)
	Housewife	2 (2.0)
	Long term sickness	2 (2.0)
	Disabled	2 (2.0)
	Never worked	1 (1.0)
Not recorded	1 (1.0)	
Patient ever smoked	Yes	93 (92.1)
	No	8 (7.9)
Diagnosis of COPD	Yes	39 (38.6)
	No	61 (60.4)
	Not recoded	1 (1.0)
Symptom cluster	Presence of breathlessness	99 (98.0)
	Presence of cough	81 (80.2)
	Presence of fatigue	99 (98.0)
Emotional status	Presence of anxiety (HADS-A ≥8)	32 (31.7)
	Presence of depression (HADS-D ≥8)	39 (38.6)
Treatment group status	Absence of further active antineoplastic therapy	12 (11.9)
	Post-curative treatment	37 (36.6)
	Follow-up palliative cancer care	52 (51.5)

364 HADS-A: Hospital Anxiety and Depression Scale-Anxiety; HADS-D: Hospital Anxiety and Depression Scale-  
365 Depression

366

**Table 2 Associations between D-12 and NRS, HADS and LCSS**

	D-12 total	D-12 physical	D-12 emotional
<b>NRS scales</b>			
NRS-average breathlessness	0.495 <sup>a</sup>	0.475 <sup>a</sup>	0.481 <sup>a</sup>
NRS-worst breathlessness	0.514 <sup>a</sup>	0.512 <sup>a</sup>	0.495 <sup>a</sup>
NRS-distress associated with breathlessness	0.611 <sup>a</sup>	0.552 <sup>a</sup>	0.642 <sup>a</sup>
NRS-ability to cope with breathlessness	-0.165	-0.139	-0.131
NRS-unpleasant associated with breathlessness	0.556 <sup>a</sup>	0.556 <sup>a</sup>	0.555 <sup>a</sup>
<b>HADS</b>			
HADS total	0.585 <sup>a</sup>	0.465 <sup>a</sup>	0.673 <sup>a</sup>
HADS anxiety	0.628 <sup>a</sup>	0.486 <sup>a</sup>	0.706 <sup>a</sup>
HADS depression	0.463 <sup>a</sup>	0.390 <sup>a</sup>	0.526 <sup>a</sup>
<b>LCSS total</b>	0.551 <sup>a</sup>	0.524 <sup>a</sup>	0.525 <sup>a</sup>

368 D-12: Dyspnoea-12; NRS: Numerical Rating Scale; HADS: Hospital Anxiety and Depression Scale; LCSS: Lung

369 Cancer Symptom Scale

370 a: significant at 0.01

371

372

**Table 3 Factor analysis for the D-12 items**

D-12 items	Factor 1 (Physical component)	Factor 2 (Emotional Component)
<b>D12-1</b> My breath does not go in all the way	<b>0.684</b>	0.221
<b>D12-2</b> My breathing requires more work	<b>0.723</b>	0.345
<b>D12-3</b> I feel short of breath	<b>0.740</b>	0.242
<b>D12-4</b> I have difficulty catching my breath	<b>0.813</b>	0.313
<b>D12-5</b> I cannot get enough air	<b>0.771</b>	0.419
<b>D12-6</b> My breathing is uncomfortable	<b>0.759</b>	0.363
<b>D12-7</b> My breathing is exhausting	<b>0.697</b>	0.527
<b>D12-8</b> My breathing makes me feel depressed	0.317	<b>0.847</b>
<b>D12-9</b> My breathing makes me feel miserable	0.302	<b>0.870</b>
<b>D12-10</b> My breathing is distressing	0.460	<b>0.775</b>
<b>D12-11</b> My breathing makes me agitated	0.336	<b>0.835</b>
<b>D12-12</b> My breathing is irritating	0.348	<b>0.787</b>

373 D-12: Dyspnoea-12

374

375 **Table 4 Discriminate performance of the D-12 for HADS anxiety and depression groups\***

D-12 scores	Anxious (HADS-A $\geq$ 8)		Non-anxious (HADS-A < 8)		Depressed (HADS-D $\geq$ 8)		Non-depressed (HADS-D < 8)	
	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
<b>D-12 total</b>	32	25.0(1.5)	65	13.7 (0.9)	39	23.1 (1.4)	59	13.8(1.0)
<b>D-12 physical</b>	28	14.3 (1.0)	61	9.3 (0.6)	33	13.7 (0.8)	57	9.3 (0.7)
<b>D-12 emotional</b>	32	10.7 (0.7)	63	4.3 (0.5)	38	9.7 (0.7)	58	4.4 (0.5)

376 All differences were statistically significant at  $P < 0.001$ .

377 D-12: Dyspnoea-12; HADS: Hospital Anxiety and Depression Scale; HADS-A: Hospital Anxiety and Depression  
378 Scale-Anxiety; HADS-D: Hospital Anxiety and Depression Scale-Depression

379 Note: D-12 total and all subscale score differences between anxious and non-anxious patients, and D-12 total and  
380 emotional score differences between depressed and non-depressed patients were tested by Mann-Whitney U  
381 test, while D-12 physical score difference between depressed and non-depressed patients was analysed by  
382 Independent-samples t-test, based on the normality test results as measured by Shapiro-Wilk approach.

383

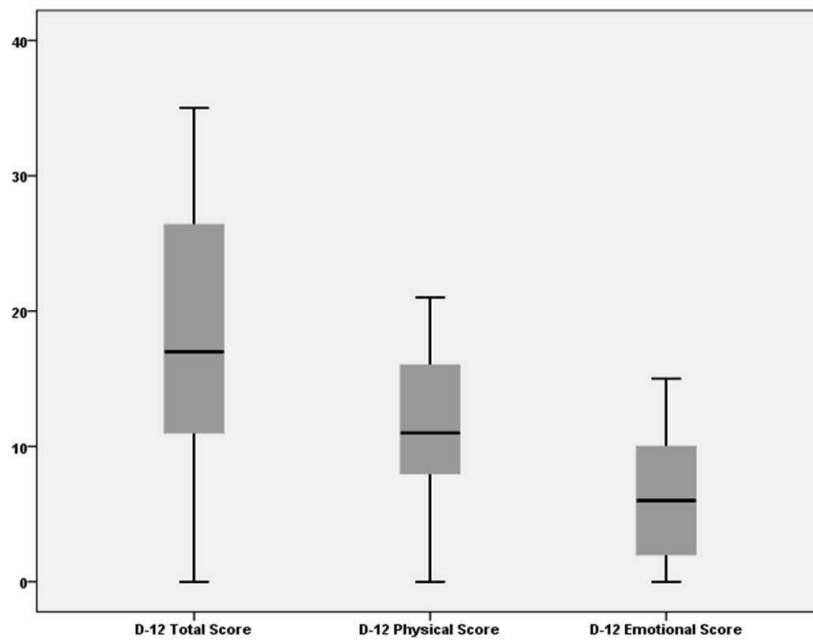
384 **Table 5 Discriminate performance of the D-12 between patients with and without COPD**

D-12 scores	COPD patients		Non-COPD patients		P value
	n	Mean (SE)	n	Mean (SE)	
<b>D-12 total<sup>a</sup></b>	39	20.7 (1.5)	61	15.7 (1.1)	0.012
<b>D-12 physical<sup>b</sup></b>	36	12.7 (0.9)	54	9.7 (0.7)	0.007
<b>D-12 emotional<sup>a</sup></b>	37	8.0 (0.8)	60	5.6 (0.6)	0.015

385 D-12: Dyspnoea-12

386 a:Mann-Whitney U test; b:Independent-samples t-test

387

388 **Figure**

389

390

391

**Figure 1 Distribution of D-12 total and component scores**

D-12: Dyspnoea-12

