

**Manuscript type:** Original Article

DOI: 10.5152/TurkThoracJ.2019.180194

**Title: Does Nutritional Risk Screening 2002 Correlate with Dyspnea Status of Patients with GOLD Stage C-D Chronic Obstructive Pulmonary Disease?**

**Short Title: Malnutrition risk screening in COPD patients**

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**Received:** 03.12.2018

**Accepted:** 18.01.2019

**Cite this article as:** Ogan N, Yıldırım F, Süzen B, et al. Does Nutritional Risk Screening 2002 Correlate with Dyspnea Status of Patients with GOLD Stage C-D Chronic Obstructive Pulmonary Disease? Turk Thorac J 2019; DOI: 10.5152/TurkThoracJ.2019.180194

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## Abstract

**Objectives:** Dyspnea is a prominent symptom of chronic obstructive pulmonary disease (COPD) and patients with GOLD Stage C-D often complain of dyspnea, but the relationship between their dyspnea level and their nutritional status and has not been established. The aim of this study was to evaluate the dyspnea levels and nutritional status of stable COPD patients in outpatients clinic.

**Methods:** Medical records including mMRC (Modified Medical Research Council) Dyspnea Scale and nutritional status of 41 patients investigated in the study. Mean age of patients was  $71.7 \pm 9.2$  years. The Nutritional Risk Screening 2002 (NRS-2002) tool, body mass index (BMI) and mid-upper arm circumference were used to evaluate their nutritional status. We used correlation analysis to display the relationship between NRS-2002 score and mMRC, COPD stage, biochemical and anthropometric parameters indicating nutritional status of patients.

**Results:** Out of the 41 COPD patients 87.8% (36) were men, and 12.2% (5) were women. GOLD stages of the patients were 29.3% stage C and 70.7% stage D. Risk of malnutrition (NRS $\geq$ 3) were detected in 48.8% of the patients, whereas 51.2% (NRS<3) were not. Mid-upper arm circumference of patients with risk was lower ( $25.6 \pm 3.2$  vs  $29.9 \pm 2.7$  cm,  $p=0.032$ ). The NRS-2002 had a positive correlation with mMRC ( $r=0.351$ ,  $p=0.024$ ). There was a statistically significant negative correlation between NRS-2002 and mid-upper arm circumference ( $r=0.604$ ,  $p<0.0001$ ). Also there was a negative correlation between BMI and mid-upper arm circumference ( $r=0.699$ ,  $p<0.0001$ ).

**Conclusion:** Malnutrition risk was common in stable COPD patients in outpatients, this seems to adversely affect their dyspnea level. Therefore, while clinicians plan the treatment of COPD patients in outpatient clinics, their evaluation the nutritional status of patients and taking precautions accordingly may contribute to the reduction of shortness of breath which is one of the most important symptoms of the disease.

**Keywords:** COPD, malnutrition, nutritional status, Nutritional Risk Screening, mMRC

## Introduction

Chronic obstructive pulmonary disease (COPD) is an important preventable cause of morbidity and mortality among all diseases in the world. In our country, the prevalence of COPD is estimated to be 19.1% according to the Turkey-BOLD Study [1] and mortality of COPD is about 7.1 %. This prevalence is close to European countries [2-4]. Malnutrition coexists in a significant proportion of COPD patients, one-fifth of patients have at least one of the weight loss, protein or caloric malnutrition. It was also commonly seen in COPD patients followed in outpatient clinics [5]. Its prevalence is

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increasing as the disease stage progresses. Nutritional status of COPD patients have been mostly investigated in hospitalised patients. Also the prevalence of malnutrition in COPD outpatients is reported to be high with up to 45% of outpatients said to be at risk [6]. But it is usually overlooked during the management of COPD patients in outpatients clinics.

Patients with GOLD Stage C-D COPD often complain of dyspnea, and also malnutrition is oftenly seen in COPD patients who have progressive chronic inflammation and frequent exacerbation. Detection of malnutrition in COPD patients can be difficult because there is no gold standard method or questionnaire for this up to now. Although the prevalence of malnutrition has been studied frequently in patients with COPD, its relation with patients' dyspnoea levels has not been investigated much.

In this study, we assessed the nutritional status of outpatients with stable COPD by investigating various anthropometric and biochemical parameters and we aimed to reveal whether there is a relationship between dyspnoea levels and nutritional status markers in patients with stable COPD.

### **Material and Methods**

We included patients with COPD Stage C-D who admitted to outpatient clinic of xxxx University Faculty of Medicine Hospital, Department of Pulmonary Medicine between December 2017 and June 2018. The prospectively collected and recorded data were evaluated retrospectively. Our local ethical board for the clinical researches approved the study protocol (Decision no:2018/106/6). Written informed consent was obtained from all the patients.

In the study population COPD diagnosis was made according to the Global Initiative for Obstructive Lung Disease (GOLD) guideline. The diagnosis of COPD was made if forced expiratory volume in 1 second/forced vital capacity (FEV<sub>1</sub>)/FVC was <70% in the pulmonary function test (PFT). Also in patients with the symptoms consistent with COPD, disease starting after 40 years of age, smoking history of at least 10 packs / year or exposure to irritant or toxic gases or exposure to biomass were sought. By using exacerbation history and modified Medical Research Council (mMRC) dyspnea scale of patients GOLD categories were determined in four groups with increasing severity (A, B, C, and D) [7]. Patients having stage C and D were included in study. All patients had stable COPD, they had no any COPD exacerbation for the last 6 months.

Nutritional screening and assessment were made by using the three-component NRS 2002 Questionnaire [8]. NRS-2002 was developed for malnutrition risk screening in hospitalized patients within the first 48 hours following admission and it was proposed by the European Society for Clinical Nutrition and Metabolism (ESPEN). This tool includes three components: The first component assesses the nutritional status across three separate items: BMI categories [20.5 kg/m<sup>2</sup>], weight loss categories [>5% in 3 months, >5% in 2 months and >5% in 1 month (>15% in 3 months)] and food intake as a proportion of the normal requirement in the preceding week (0%-25%, 25%-50%, 50%-75% and >75%). The second and third components assess disease severity and age,

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respectively, with all subjects over 70 years being given an additional weighting. The BMI cut off value for diagnosing malnutrition was 18.5 kg/m<sup>2</sup> [8].

Dyspnea status of patients in daily life was evaluated by mMRC (Modified Medical Research Council) Dyspnoea scale. This scoring is a questionnaire that is scored the dyspnea level on the range between no dyspnea (Grade 0) and almost complete disability (Grade 4) [9].

Demographic data, smoking habits, pulmonary function tests, severity of COPD, anthropometrics measurements [Body mass index (BMI), mid-arm circumference], blood biochemical indicators of nutrition, mMRC dyspnea scale and NRS-2002 scores of patients recorded. We compared the patients with nutritional risk ( $\geq 3$ ) and without nutritional risk ( $< 3$ ).

### Statistical analysis

All statistical analyses were performed using SPSS for Windows (Version 21.0, SPSS Inc.). We performed a power analysis to calculate sample size, and 41 patients were found to be necessary for a significance level of 0.05. All tests were interpreted using a significance level of  $p < 0.05$ . Kolmogorov-Smirnov test was used to determine whether the data were distributed normally. Descriptive statistical methods (mean, standard deviation, median, frequency) and Student's t-test were used to compare percentage of groups. Chi-square test was used to determine the relationship between categorical variables and correlation analysis was used for the relationship between mMRC and nutritional status variables.

### Results

We included 41 patients with the mean age of  $71.7 \pm 9.2$  years and 87.8% ( $n=36$ ) of patients were male. Out of 75.6% patients were older than 65 years-old age. Majority of our patients were at GOLD Stage 4 (70.7%). Patients with risk of malnutrition ( $NRS \geq 3$ ) were 48.8% of the patients, whereas 51.2% ( $NRS < 3$ ) were not. Mean mMRC score of patients was  $2.0 \pm 0.7$  while mean NRS-2002 was  $2.5 \pm 1.2$ . The findings regarding the patients' age, smoking status, exacerbation status, GOLD stages, mMRC, pulmonary function tests, NRS scores, and anthropometrics and biochemical parameters are given in Table 1.

The COPD patients with risk of malnutrition and patients without risk were similar in terms of age, gender, and smoking habits. FEV1 (% predicted) was lower in patients at risk of malnutrition than those without malnutrition ( $43.8 \pm 13.1$  vs  $45.2 \pm 15.6$ ;  $p=0.041$ ) but forced vital capacity (FVC) and the FEV1/FVC ratio were similar ( $p > 0.05$ ). The NRS-2002 evaluation showed that the risk of malnutrition was greater in patients with stage D and lower in stage C according to the GOLD criteria ( $p=0.05$ ). According to NRS-2002 components, BMI of the patients with malnutrition risk was lower than patients without malnutrition risk ( $23.5$  vs  $28.7$  kg/m<sup>2</sup>,  $p=0.036$ ). Also mid-arm circumferences, albumin and LDL levels were significantly lower in patients with nutritional risk ( $p < 0.05$ ). The mMRC scores of patients with malnutrition risk were significantly higher ( $2.3 \pm 0.7$  vs  $1.8 \pm 0.7$ ;  $p=0.033$ ) (Table 2).

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The NRS-2002 had a positive correlation with mMRC ( $r=0.351$ ,  $p=0.024$ ) and GOLD stage ( $r=0.379$ ,  $p=0.015$ ). There was a statistically significant negative correlation between NRS-2002 and mid upper arm circumference ( $r=0.699$ ,  $p<0.001$ ). However, the NRS-2002 score was not significantly correlated with blood biochemical indicators (Folat, albumin, vit B12, LDL, HDL, phosphorus)(Table 3).

**Table 1: Basic characteristics, functional and nutritional status of patients**

Variables	N=41 (%)	Mean±SD
Gender (Male/female)	36/5 (87.8/12.2)	-
Age (years)	-	71.7±9.2
58-64	10.0/24.4	-
65-74	17.0/41.5	-
≥75	14.0/34.1	-
Smoking habit		
Never smoked	4.0 (9.8)	-
Current smoker	34.0 (82.9)	-
Ex smoker	3.0 (7.3)	-
Smoking history (package/years)		39.9±20.3
Number of exacerbations (per year)		1.9±1.2
mMRC Score	-	2.0±0.7
1	10.0/24.4	
2	22.0/53.7	
3	8.0/19.5	
4	1.0/2.4	
Severity of COPD		
GOLD stage C	12.0/29.3	-

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GOLD stage D	29.0/70.7	-
Pulmonary Function Tests		
FVC (%)	-	63.0±15.5
FVC (L)	-	2.3±0.8
FEV1 (%)	-	44.5±14.3
FEV1 (L)	-	1.3±0.6
FEV1/FVC (%)	-	53.6±10.2
Nutritional Risk Score (NRS) 2002		
NRS-2002 <3 (without risk)	20.0/48.8	
NRS-2002 ≥3 (with risk)	21.0/51.2	
NRS according to COPD severity		
GOLD stage C		1.7±1.4
GOLD stage D		2.8±1.1
Anthropometrics		
BMI (kg/m <sup>2</sup> )		26.1±4.8
Mid-arm circumference (cm)		27.8±3.6
Blood biochemical indicators		
Folat (ng/mL)	-	3.7±0.7
Vit B12 (pg/mL)	-	260.7±87.2
Albumin (gr/dL)	-	0.8±0.1
LDL (mg/dL)	-	3.4±0.6
HDL (mg/dL)	-	99.4±32.1

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Phosphorus (mg/dL)	-	41.0±13.0
Sistolic Pulmonary arterial pressure (mmHg)	-	31.4±12.6

Abbreviations: mMRC:Modified Medical Research Council, COPD:Chronic obstructive pulmonary disease, GOLD: Global Initiative for Obstructive Lung Disease, FEV1:Forced expiratory volume in 1 second,FVC:forced vital capacity, NRS:Nutritional Risk Screening, BMI:Body mass index, LDL: Low density lipoprotein, HDL:High density lipoprotein

**Table 2: Comparison of patients with or without nutritional risk**

Characteristics	With Nutrition Risk (N=20) (Mean±SD)	Without Nutritional Risk (N=21) (Mean±SD)	p
Gender (Male/female) (N,%)	18/2 (90/10)	18/3 (85.7/14.3)	0.524
Age (years)	74.6±9.0	68,9±8,7	0.136
Age distribution (N,%)			
58-64	4.0/20.0	6.0/28.6	0.393
65-74	7.0/35.0	10.0/47.6	0.308
≥75	9.0/45.0	5.0/23.8	0.136
Smoking habit (N,%)			0.805
Never smoked	2.0/10.0	2.0/9.5	
Current smoker	16.0/80.0	18.0/85.7	
Ex smoker	2.0/10.0	1.0/4.8	
Smoking history (package/years)	42.2±23.0	35.7±17.2	0.343
Number of exacerbations (per year)	2.1±1.3	1.7±1.1	0.148
mMRC Score	2.3±0.7	1.8±0.7	0.033
Pulmonary Functions			
FVC (%)	60.9±15.2	64.9±15.9	0.151

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FVC (L)	2.3±0.8	2.3±0.8	0.06
FEV1 (%)	43.8±13.1	45.2±15.6	0.041
FEV1 (L)	1.3±0.7	1,3±0,6	0.046
FEV1/FVC (%)	53.9±10.1	53.5±10.5	0.131
Severity of COPD (N,%)			0.05
GOLD stage C	3.0/15.0	9.0/42.6	
GOLD stage D	17.0/85.0	12.0/57.4	
Anthropometrics			
BMI (kg/m <sup>2</sup> )	23.5±4.1	28.6±4.3	0.036
Mid-arm circumference (cm)	25.6±3.2	29.9±2.7	0.003
Blood biochemical indicators			
Folat (ng/mL)	3.8±0.8	3.6±0.6	0.02
Vit B12 (pg/mL)	274.6±78.8	247.5±94.4	0.06
Albumin (gr/dL)	3.2±0.4	3.5±0.5	0.02
LDL (mg/dL)	96.4±37.1	102.2±27.1	0.03
HDL (mg/dL)	44.4±11.7	38.0±13.6	0.011
Phosphorus (mg/dL)	3.3±0.6	3.4±0.6	0.146
Sistolic Pulmonary Arterial Pressure (mmHg)	33.3 ±11.6	29.5±13.4	0.139

Abbreviations: mMRC:Modified Medical Research Council, FEV1:Forced expiratory volume in 1 second, FVC:forced vital capacity, COPD:Chronic obstructive pulmonary disease, GOLD: Global Initiative for Obstructive Lung Disease, BMI:Body mass index, LDL: Low density lipoprotein, HDL:High density lipoprotein

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**Table 3: Correlation coefficients (r) of NRS scores with anthropometric, biochemical parameters and pulmonary functions**

Variables	r coefficient	p
Mid-arm circumferences	-0.595	<0.001
GOLD Stage	0.379	0.015
mMRC	0.351	0.024
FEV1(L)	0.847	0.031
Folat	0.276	0.080
Vit B12	0.588	0.087
Albumin	-0.147	0.358
Phosphorus	-0.071	0.661
Blood Urea Nitrogen	0.221	0.164
HDL	0.235	0.138
LDL	-0.081	0.615

*Abbreviations: BMI: Body mass index, GOLD: Global Initiative for Chronic Obstructive Lung Disease, mMRC: The Modified Medical Research Council, HDL: High density lipoprotein, LDL: Low density lipoprotein*

## Discussion

In our study, a significant correlation was found between the ESPEN NRS-2002 malnutrition risk assessment score and mMRC dyspnea score in the stable GOLD stage C and D COPD patients. Our data provided evidence of a relationship between the symptom level and their nutritional status of the patients with COPD.

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COPD is characterised with progressive chronic systemic inflammation with frequent exacerbations and oftenly accompanied by malnutrition. Many factors especially cigarette smoking, systemic inflammation by TNF- $\alpha$  and neutrophils can cause malnutrition despite adequate food intake. Therefore, the presence of malnutrition in COPD patients may play an important role in disease progression and control of symptoms.

Several methods have been used to screen for the presence of malnutrition in COPD patients [10,11]. To the best of our knowledge, this is the first study from our country that examined NRS-2002 in COPD patients followed in outpatient clinics. Most of the previous studies investigating the nutritional status of COPD patients have used other nutritonal risk scales. In our study, we evaluated the nutritional status of the patients with NRS-2002 test. NRS-2002 test is used for hospitalised patients up to now. Arslan et al [12] determined the relationship between quality of life and nutritional status in hospitalized COPD patients by using NRS-2002 tool and the Short Form-36 (SF-36) questionnaire. Out of 55.6 % of their COPD patients had the malnutrition risk, this ratio was very close to our 51.2% result. SF-16 values were found lower in patients with risk of malnutrition than in patients with no malnutrition risk in their study. Their patients different from our patients were hospitalised patients. We used mMRC dyspnea scale instead of SF-16. There are studies showing the association between quality of life and Mmrc scale both in COPD patients and other lung diseases whose main pulmonary symptom is dyspnea [13,14].

The majority of our patients with risk of malnutrition were GOLD stage D. This situation also shows that nutritional status deteriorates as GOLD stage increases. Benedik et al [15] used to Mini Nutritional Assessment (MNA) questionnaire in 108 hospitalised patients. Similar to our study 85% of their COPD patients were severe or very severe COPD. Out of 55% were at risk of malnutrition and MNA score decreased over GOLD stage ( $p=0.02$ ). Dispnea levels of patients according to mMRC dispnea scale were found to be high in patients with malnutiritoral risk ( $3.3\pm 1.2$  vs  $3.1\pm 0.9$ ,  $p=0.037$ ) [15].

Malnutrition is associated with poor prognosis and severe airway disease in COPD. In previous studies, FEV1 was found to be lower in malnourished patients [16,17]. In our study, we found a positive correlation between NRS-2002 test results and FEV1% values. Patients with malnutrition risk were found to have a lower FEV1 (L) value.

Scichilone et al researched the association between MNA scores and dyspnea perception of COPD patients attending to outpatients clinic as our study. All of their patients were older than 60 years-old age. They found that patients with malnutrition risk had higher mMRC dispnea scores eventhough their BMI were within the normal ranges. Their ordinal regression analysis revealed that MNA was the only independent factor to predict mMRC  $p=0.01$ ) [18]. Out of 75.6% of our patients were older than 65 years-old age, mMRC scores of patients with mlanutrition risk was higher than patients without risk ( $2.3\pm 0.7$  vs  $1.8\pm 7.0$ ;  $p=0.033$ ) in our study. Also we found a positive correlation between mMRC and NRS-2002 score.

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In the study of Lainscak et al [15] it was observed that patients with COPD who had malnutrition had low upper middle arm and shank circumference. In our study, mid-arm circumferences of COPD patients at risk of malnutrition was lower than patients without malnutrition risk. In accordance with the literature; as the nutritional status deteriorated, a fall was observed in the upper-middle arm circumference and the lowest values were found in patients with malnutrition risk. In addition, a significant negative correlation was found between NRS-2002 score and upper-middle arm circumference in all study group.

Recently Marco et al [19] investigated the COPD patients with ESPEN malnutrition definition. Similar to our study their patients population composed of COPD patients in the stable stage. They prospectively investigated 118 COPD patients free of exacerbations and/or hospital admissions in the previous two months. In their study, they made a malnutrition nutritional evaluation according to the definition of ESPEN and parameters including unintentional weight loss, body mass index and lean mass index (FFMI). They evaluated the body composition of the patients by bioimpedance analysis. They found the prevalence of malnutrition as 24.6%. Malnutrition was found to be associated with increased mortality risk (HR=3.9 [95% CI: 1.4-10.62]) in their study [19]. This study with the similar result shows nutritional status of the COPD patients should be evaluated not only in the hospitalised patients but also in outpatients clinics.

In conclusion, COPD patients were found to have a high risk of malnutrition that adversely affects their dyspnea. Nutrition is an important factor affecting the disease symptoms, and nutritional improvement is one of the effective measures to relieve the symptoms of COPD. Therefore, while clinicians plan the medical treatment of COPD patients in outpatient clinics, their evaluation the nutritional status of patients and taking precautions accordingly may contribute to the reduction of shortness of breath which is one of the most important symptoms of the disease.

### Conflicts of interest

Authors declared no conflict of interest.

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