

**Title:** Determinants of exercise-induced oxygen desaturation including pulmonary emphysema in COPD: results from the ECLIPSE study

**Running title:** Oxygen desaturation and emphysema in COPD

Vasileios Andrianopoulos<sup>1, 2§</sup>

Bartolome R. Celli<sup>3</sup>

Frits M.E. Franssen<sup>1</sup>

Victor M. Pinto-Plata<sup>4</sup>

Peter M.A Calverley<sup>5</sup>

Lowie E.G.W Vanfleteren<sup>1,14</sup>

Ioannis Vogiatzis<sup>6</sup>

Jørgen Vestbo<sup>7</sup>

Alvar Agusti<sup>8</sup>

Per S. Bakke<sup>9</sup>

Stephen I. Rennard<sup>10</sup>

William MacNee<sup>11</sup>

Ruth Tal-Singer<sup>12</sup>

Julie C. Yates<sup>13</sup>

Emiel F.M. Wouters<sup>1,14</sup>

Martijn A. Spruit<sup>1,15</sup>

## **Affiliations**

<sup>1</sup>Department of Research and Education; CIRO+, Centre of Expertise for Chronic Organ Failure; Horn; the Netherlands

<sup>2</sup>Department of Respiratory Medicine and Pulmonary Rehabilitation; Schoen Klinik Berchtesgadener Land; Schoenau am Koenigssee, Germany

<sup>3</sup>Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

<sup>4</sup>Department of Respiratory Medicine, School of Clinical Science, University of Liverpool, United Kingdom

<sup>5</sup>Institute of Ageing and Chronic Disease, University Hospital Aintree, Liverpool, United Kingdom

<sup>6</sup>Department of Physical Education and Sport Sciences, National and Kapodistrian University of Athens, Greece

<sup>7</sup>Centre for Respiratory Medicine and Allergy, University of Manchester, UK

<sup>8</sup>Respiratory Institute, Hospital Clinic, IDIBAPS, University of Barcelona, CIBERES, Barcelona, Spain

<sup>9</sup>Department of Clinical Science, University of Bergen, Bergen, Norway

<sup>10</sup>Pulmonary and Critical Care Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA

<sup>11</sup>Medical Research Council Centre for Inflammation Research, University of Edinburgh The Queen's Medical Research Institute, Edinburgh, United Kingdom

<sup>12</sup>GSK Research and Development, King of Prussia, Philadelphia, Pennsylvania, USA

<sup>13</sup>GSK Research Triangle Park, North Carolina, USA

<sup>14</sup>Department of Respiratory Medicine, Maastricht University Medical Centre (MUMC+),  
Maastricht, the Netherlands

<sup>15</sup>REVAL – Rehabilitation Research Center, BIOMED – Biomedical Research Institute,  
Faculty of Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium

**Email addresses of authors:**

Vasileios Andrianopoulos: [vasilisandrianopoulos@ciro-horn.nl](mailto:vasilisandrianopoulos@ciro-horn.nl)

Bartolome R. Celli: [bcelli@copdnet.org](mailto:bcelli@copdnet.org)

Frits M.E. Franssen: [fritsfranssen@ciro-horn.nl](mailto:fritsfranssen@ciro-horn.nl)

Victor M. Pinto-Plata: [vpinto@copdnet.org](mailto:vpinto@copdnet.org)

Peter M.A Calverley: [pmacal@liverpool.ac.uk](mailto:pmacal@liverpool.ac.uk)

Lowie E.G.W Vanfleteren: [lowievanfleteren@ciro-horn.nl](mailto:lowievanfleteren@ciro-horn.nl)

Ioannis Vogiatzis: [gianvog@phed.uoa.gr](mailto:gianvog@phed.uoa.gr)

Jørgen Vestbo: [Jorgen.Vestbo@manchester.ac.uk](mailto:Jorgen.Vestbo@manchester.ac.uk)

Alvar Agusti: [alvar.agusti@clinic.ub.es](mailto:alvar.agusti@clinic.ub.es)

Per S. Bakke: [per.bakke@med.uib.no](mailto:per.bakke@med.uib.no)

Stephen I. Rennard: [srennard@unmc.edu](mailto:srennard@unmc.edu)

William MacNee: [w.macnee@ed.ac.uk](mailto:w.macnee@ed.ac.uk)

Ruth Tal-Singer: [Ruth.M.Tal-Singer@gsk.com](mailto:Ruth.M.Tal-Singer@gsk.com)

Julie C. Yates: [julie.c.yates@gsk.com](mailto:julie.c.yates@gsk.com)

Emiel F.M. Wouters: [e.wouters@mumc.nl](mailto:e.wouters@mumc.nl)

Martijn Spruit: [martijnspruit@ciro-horn.nl](mailto:martijnspruit@ciro-horn.nl)

## §Corresponding author information

Vasileios Andrianopoulos, PhD

Department of Respiratory Medicine and Pulmonary Rehabilitation; Schoen Klinik

Berchtesgadener Land; Schoenau am Koenigssee, Germany. Tel: +49 (0)8652 93-1540

Email: [VAndrianopoulos@schoen-kliniken.de](mailto:VAndrianopoulos@schoen-kliniken.de)

## Abbreviations list

ADO: Age, Dyspnoea, airflow Obstruction index

BMI: Body mass index

BODE: Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity index

COPD: Chronic Obstructive Pulmonary Disease

FEV<sub>1</sub>: Force expiratory volume in 1 second

FEV<sub>1</sub>/FVC: The ratio (r) of forced expiratory volume in 1 second and forced vital capacity

FFMI: Fat free mass index

FVC: Force vital capacity

mMRC: modified Medical research council dyspnoea scale.

ROC: Receiver operating characteristics curves

SGRQ: Saint George's Respiratory Questionnaire

SpO<sub>2</sub>: Saturation of peripheral oxygen

QCT-emphysema: Quantified by Computed-Tomography emphysema

6MWD: Six-minute walk distance

6MWT: Six-minute walk test

**Key Words:** 6MWD, EID, ADO index, emphysema, computed tomography, imaging

## Abstract

Exercise-induced oxygen desaturation (EID) is related to mortality in patients with chronic obstructive pulmonary disease (COPD). We investigated: (1) the prevalence of EID; (2) the relative-weight of several physiological determinants of EID including pulmonary emphysema, and (3) the relationship of EID with certain patients' clinical characteristics.

Data from 2050 COPD patients (age:  $63.3 \pm 7.1$  years;  $FEV_1$ :  $48.7 \pm 15.7\%$  pred.) were analyzed. The occurrence of EID ( $SpO_2 \leq 88\%$ ) at the six-minute walking test (6MWT) was investigated in association with emphysema quantified by computed-tomography (QCT), and several clinical characteristics.

435 patients (21%) exhibited EID. Subjects with EID had more QCT-emphysema, lower exercise capacity and worse health-status (BODE, ADO indexes) compared to non-EID. The occurrence of EID was progressively increased across emphysema-degrees in GOLD II ( $\leq 9$ -fold) but this increase was lower in GOLD III-IV. Determinant of EID were obesity ( $BMI \geq 30 \text{ kg/m}^2$ ), low  $FEV_1$  ( $\leq 44\%$  pred.), moderate or worse emphysema, and low baseline  $SpO_2$  ( $\leq 93\%$ ). Linear regression indicated that each 1-point increase on the ADO-score independently elevates odds ratio ( $\leq 1.5$  fold) for EID.

About one in five COPD patients in the ECLIPSE cohort presents EID. Emphysema severity is more related to EID in GOLD II compared to GOLD III-IV. In addition, obesity, airflow obstruction, and low baseline oxygen saturation increase the odds for EID. Emphysematous patients with high ADO-score should be monitored for EID.

## 1. Introduction

Exercise-induced oxygen desaturation (EID), as defined by fall in oxygen saturation to 88% or lower during exercise<sup>1,2</sup>, can occur in patients with Chronic Obstructive Pulmonary Disease (COPD), even in those without resting hypoxemia.<sup>3-5</sup> Yet, their physiological determinants and clinical consequences are still subject of debate. In general, patients with EID are characterized by severe airflow limitation, low diffusing carbon monoxide capacity (DLCO), reduced resting arterial oxygenation<sup>6-9</sup> and the presence of emphysema<sup>10-12</sup>. In addition, EID is also related to numerous variables that include the rate of lung function decline and health status<sup>13</sup>, physical activity<sup>14</sup>, and the outcomes of hospitalization as well as mortality.<sup>15,16</sup> The determinants of EID, however, have not been validated in a large cohort of COPD patients followed up prospectively. The design and size of the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study offers a unique opportunity to overcome these limitations.<sup>17</sup>

Herein, we investigated in the ECLIPSE: (1) the prevalence of EID in COPD; (2) the relative weight of several physiological determinants of EID in COPD, particularly the severity of airflow limitation and the presence of emphysema as defined by quantitative computed tomography (QCT) analysis<sup>18-20</sup>; and, (3) the relationship of EID with certain patients' clinical characteristics.

## 2. Material and Methods

### 2.1 Design and participants

The ECLIPSE study (Clinicaltrials.gov identifier NCT00292552; GSK study code SCO104960) was a 3-year non-interventional longitudinal prospective study, as described elsewhere.<sup>17</sup>

In brief, individuals (age: 40-75 years) were recruited to ECLIPSE if they had a smoking history of  $\geq 10$  pack-years and a diagnosis of COPD.<sup>21</sup> We excluded subjects with resting hypoxemia (as defined by  $\text{SpO}_2\%$  pre-walk  $\leq 88\%$ ) from this analysis. The ECLIPSE study was carried out in accordance with the Declaration of Helsinki and good clinical practice guidelines, and was approved by the ethics committees of participating centers. The Institutional Review Boards of all participating institutions approved the study and all participants provided written informed consent. Data from the ECLIPSE study have been published before<sup>16, 22-24</sup> but the current analysis, which is mostly focus on EID in association with the severity of emphysema, is novel and, therefore, complements previous reports.

## **2.2 Subject characterization**

Demographic and physiological characteristics, level of dyspnoea (using the modified Medical Research Council (mMRC) dyspnoea scale)<sup>25</sup>, measurements of lung function (post-bronchodilator spirometry and lung volumes), QCT-emphysema degrees, health status (using the St. George's Respiratory Questionnaire (SGRQ))<sup>26</sup>, and data from 6MWT were used in this analysis. Fat mass and fat free mass were determined using bioelectrical impedance (Bodystat 1500). The fat free mass index (FFMI,  $\text{kg}/\text{m}^2$ ) was calculated as the mass (kg) divided by the squared height ( $\text{m}^2$ ) and the body mass index (BMI,  $\text{kg}/\text{m}^2$ ) was calculated as weight (kg) divided by squared height ( $\text{m}^2$ ). Furthermore, the following multidimensional COPD indices were calculated for the whole cohort; (1) the ADO index<sup>27</sup>, which includes age, dyspnoea by the MRC, and  $\text{FEV}_1\%$ , and (2) the BODE index<sup>28</sup>, which incorporates dyspnoea by the MRC, BMI,  $\text{FEV}_1\%$ , and exercise capacity as measured by 6-minute walking distance (6MWD).

### **2.3 CT imaging**

All subjects underwent a low-dose volumetric computed tomography (CT scan) at full inspiration. Scans were obtained using multi-detector row CT scanners (120 kVp, 40 mAs) and were reconstructed using contiguous 1.00 mm or 1.25 mm slice thickness and an intermediate spatial frequency reconstruction algorithm. The radiation dose was estimated to be 1.67 mSv per CT study or 5 mSv for the entire ECLIPSE protocol. All CT scans were sent for evaluation at the central imaging unit at the University of British Columbia (Vancouver, BC, Canada).<sup>29</sup> All CT scans were analysed by the use of Pulmonary Workstation 2.0 software (VIDA Diagnostics, Coralville, IA, USA) and the severity of emphysema was quantified in CT scans (QCT) by two radiologists using the % of lung pixels that were low attenuation areas (%LAA) defined as being below 950 Hounsfield Units (density mask technique).<sup>18, 20, 30</sup> The degree of QCT-emphysema was classified according to a 5-scale score as absent-trivial: <5% (scores 0-1), mild: 5-25% (score 2), moderate: 25-50% (score 3), or severe to very severe: >50% (scores 4-5).<sup>29</sup>

### **2.4 Six-minute walk test (6MWT)**

The 6MWT was performed according to international recommendations.<sup>31</sup> Briefly, participants were asked to walk indoors in a flat, straight, 30-meter walking course supervised by a well-trained researcher. A practice 6MWT was not undertaken. Patients were encouraged using standardized encouragement every minute of the 6MWT.<sup>1</sup> Resting (pre-walk) and post SpO<sub>2</sub> were assessed using a pulse oxymeter with a finger probe. A modified Borg scale was used to quantify the levels of dyspnoea and fatigue perceived by patients at the beginning and end of the test. All subjects included in the

analysis were non-hypoxemic at rest ( $\text{SpO}_2$  pre-walk  $\geq 89\%$ ). EID was defined as a fall of oxygen saturation to  $\text{SpO}_2 \leq 88\%$  at the end of the test.<sup>1,2</sup>

## **2.5 Statistical analyses**

Results are reported as mean (standard deviation) or proportion (%). The statistical significance of differences between groups was assessed by analysis of variance, paired T-tests and Chi-square, as appropriate. Pearson's correlation coefficients were used to assess the bivariate relationship amongst patients' characteristics and the variables of  $\text{SpO}_2\%$  post-walk,  $\Delta\text{SpO}_2\%$  and QCT-defined emphysema. Linear regression and univariate and multivariate binary logistical regression models were used to assess individual predictors of EID. Receiver operating characteristics (ROC) curves were used to determine threshold values to predict EID. The Area Under the curve (AUC) was calculated by the trapezoidal rule and the confidence intervals of the AUC was computed by the method of DeLong.<sup>32</sup> Two-sided level of significance was set at  $P < 0.05$ . Statistical analyses were carried out using MedCalc v.12, Sigmaplot v.12 and SPSS v.19.0.

## **3. Results**

### **3.1 Subject characteristics**

Two thousand and fifty subjects ( $n=2050$ ) with COPD were included in the study. As shown in Table 1, subjects generally had severe airflow limitation, low oxygen saturation ( $\text{SpO}_2$  pre-walk), and were normal-weight to overweight. A total of 1124 subjects (55%) were assigned into GOLD III and IV while 622 subjects (33%) were

diagnosed with severe to very severe emphysema. Fifty three percent (53%) of the subjects complained of severe dyspnoea (mMRC scale  $\geq 2$ ), and 47% had severely impaired health status (SGRQ Total Score  $\geq 50$ ). Thirty six percent (36%) were current smokers (Table 1).

### *3.2 Determinants of EID*

A total of 435 subjects (21%) exhibited EID while the prevalence of EID was higher across GOLD stages (Figure 1). Subjects with EID were older with more severe airflow limitation, lower FVC, and worse mMRC dyspnoea and SGRQ total scores. Also, they were more commonly ex-smokers compared those without EID (non-EID; Table 1). Subjects with EID had a shorter walk distance (6MWD), lower pre-walk SpO<sub>2</sub> and higher pre/post-walk heart rate. In addition, EID subjects had greater increase of heart rate from baseline ( $\Delta$ HR) and more intense exertional dyspnoea compared to non-EID (Table 2). Moreover, those with EID had higher scores of the ADO index<sup>27</sup> and the BODE index<sup>28</sup> compared to non-EID subjects (Table 2).

The effect of QCT-emphysema on the lowest values of oxygen saturation levels, which defined the EID (SpO<sub>2</sub> decline  $\leq 88\%$ ) in the 6MWT, seems to be greater in GOLD stages II compared to GOLD stages III-IV (Figure 2). Occurrence of EID was increased progressively across emphysema severity in GOLD II by a factor of up to 9 but this relative increase was lower and not distinctively progressive in GOLD III-IV. Both, severity of airflow limitation and the extent of emphysema had a negative impact on the SpO<sub>2</sub> levels at the end of 6MWT.

### *3.3 Multivariate correlates of EID*

Using receiver operating characteristics (ROC) curves, the threshold values with the best specificity and sensitivity to predict EID were determined for age ( $\geq 60$  years), sex (female), BMI ( $\geq 30$  kg/m<sup>2</sup>), FEV<sub>1</sub> ( $\leq 44\%$  predicted), QCT-emphysema (moderate to very severe), resting oxygen saturation (SpO<sub>2</sub> pre-walk  $\leq 93\%$ ) and ADO index (ADO score  $\geq 6$  points; Online table 1). Univariate logistical regression analysis revealed that older age and impaired levels of FEV<sub>1</sub>, QCT-emphysema, and SpO<sub>2</sub> pre-walk were independent predictors of EID. Multivariate logistical regression model showed that only impaired levels of FEV<sub>1</sub>, QCT-emphysema, and SpO<sub>2</sub> pre-walk remained significant ( $p \leq 0.016$ ). Interestingly, BMI (obesity) reached statistical significance ( $p < 0.003$ ) for contributing EID only within this multivariate-adjusted model and not as independent determinant (Table 3).

A combination of certain clinical characteristics including obesity, moderate to very severe emphysema, severe airflow limitation (FEV<sub>1</sub>  $\leq 44\%$  pred.), and resting SpO<sub>2</sub>  $\leq 93\%$  revealed that the 81% of the subjects with all of these characteristics exhibited EID (Figure 3).

### *3.4 Relationship of ADO score with EID*

The presence of EID was related to higher ADO index<sup>27</sup> scores in EID subjects with GOLD II-III and across all the degrees of emphysema compared to those with non-EID. For each 1-point increase on the ADO score, the odds ratio for EID was independently increased by 1.5 fold while 40% of subjects with ADO  $\geq 6$  points had EID (Online table 2).

## 4. Discussion

This study provides three major observations: (1) about 20% of COPD patients included in the ECLIPSE cohort exhibited EID; (2) emphysema, severity of airflow limitation, arterial oxygen saturation at rest and obesity are associated with EID; and (3) a high ADO index is predictive of EID.

It has been previously suggested that the presence of emphysema may determine EID in COPD.<sup>11</sup> However, this is the first time that the role of emphysema was investigated in a large well-characterized COPD population (ECLIPSE cohort). In this study, emphysema in association with other determinants, such as obesity ( $\text{BMI} \geq 30 \text{ kg/m}^2$ ), have a prognostic value in the prediction of EID. Moreover, the relationship of the ADO score with EID was a novel investigation.

### 4.1 Interpretation of results

In current study, the prevalence of EID was increased across the GOLD stages (Figure 1) while the severity of airflow limitation seems to contribute to the occurrence of EID more than the grades of QCT-emphysema (Figure 2). However, the severity of emphysema was more critical for the presence of EID in subjects with GOLD II compared to those with more severe airflow limitation. Specifically, the incidence of EID in GOLD II was progressively increased across to emphysema degrees ( $\geq 9$ -fold) but this was not the case in GOLD III-IV (Figure 2). Ventilation-perfusion inequality (V/Q), which cause EID<sup>14</sup>, seems to be mostly attributed to the degree of emphysema in GOLD II but mostly related to the severity of airflow-limitation in GOLD III-IV.

In fact, impaired oxygen transport and utilization is a common consequence in both airway limitation and pulmonary emphysema, and can lead to ventilation/perfusion (V/Q) mismatch resulting in EID. Airflow limitation (impaired FEV<sub>1</sub>) that often leads to dynamic hyperinflation<sup>33, 34</sup>, and emphysema which is linked to decreased alveolar surface area and loss of elastic recoil of the lungs<sup>35, 36</sup>, can both cause V/Q inequality during exercise contributing to the presence of EID.<sup>37</sup> Indeed, the negative influence of very low FEV<sub>1</sub> (GOLD III-IV) on oxygen saturation levels, as it is reported in previous studies<sup>5, 38</sup>, might be overlapping with the contribution of severe emphysema on the occurrence of EID. Nevertheless, correlation analysis of this study indicated that emphysema as well as airflow limitation similarly correlated to the post-walk SpO<sub>2</sub> (r= -0.35 and r= 0.38, respectively, *p* <0.001; Online table 3) and this fact demonstrated that severity of emphysema can be also a major determinant of EID, especially in moderate COPD.

In this study, an important finding is that obesity was associated with the presence of EID in COPD. Previously, the association of lower SpO<sub>2</sub> with obesity has been reported for 871 emergency department patients and hospital workers.<sup>39</sup> Kapur and colleagues have also demonstrated that obesity is associated with a lower resting oxygen saturation examining a large cohort of 2.252 elderly subjects from the Cardiovascular Health Study.<sup>40</sup> In COPD, one study confirms a correlation between COPD severity with BMI and oxygen saturation using measurements of SpO<sub>2</sub> values at rest.<sup>41</sup> To the best of our knowledge, our findings revealed for the first time a potential relationship between obesity and EID during the 6MWT in subjects with COPD. The direct physiological mechanism underlying the effect of obesity on EID is complex; however, obesity and EID

could be related to low baseline SpO<sub>2</sub>, which can be considered as one of the major determinant of EID.<sup>5, 8</sup>

In this study, we also investigated the relationship of the ADO index<sup>27</sup> and EID. Previously, the prognostic value of the ADO index regarding to the risk of exacerbation and death have been reported, however, ADO prognostic value of EID has never been investigated.<sup>42, 43</sup> Multidimensional indices for the prognosis of oxygen desaturation have been proposed by Cutaia and colleagues<sup>44</sup> who suggested that patients with an increased BODE index<sup>28</sup> ( $\geq 7$  points) should be evaluated for oxygen desaturation during daily activities.<sup>44</sup> In our analysis, the selection of ADO index<sup>27</sup> for screening EID was based on the fact that exercise or a 6MWT is not required in order to record a score for this clinical index. Patients with high score of ADO index<sup>27</sup> ( $\geq 6$  points) presented a greater occurrence of EID (40% vs 19%;  $p < 0.001$ ; table 2). This can be attributed to severe airflow limitation and/or extended emphysema which was common in those patients with high ADO scores. Subjects with EID in GOLD II-III had higher ADO scores compared to non-EID, but this was not true in GOLD IV, while ADO scores were also greater in subjects with EID across the emphysema severity (Online figure 1). However, we did not include ADO index in our multivariate logistical model as age and FEV<sub>1</sub>, which are the main elements of ADO index, were already included as independent determinants in this statistical analysis.

In our multivariate logistical regression model, obese subjects with an impaired FEV<sub>1</sub> ( $\leq 44\%$ ), moderate to very severe emphysema, and low pre-walk SpO<sub>2</sub> ( $\leq 93\%$ ) have higher odds for EID (Table 3 and Figure 3). As it was expected, the role of emphysema in EID was critical and therefore emphysematous patients should be screened for EID, especially those with high ADO scores.

## 4.2 Strengths and weaknesses

There are certain limitations to our study. First, the 6MWT screening was performed only once at baseline, while the 2014 ERS/ATS technical standard for field walking tests suggests the conduct of two 6MWT.<sup>1</sup> Second, EID was defined based on the SpO<sub>2</sub> at the end of the test (SpO<sub>2</sub> post) and not the SpO<sub>2</sub> nadir which can lead to an underestimation of the patients who exhibit EID during the 6MWT. Even though SpO<sub>2</sub> post and the SpO<sub>2</sub> nadir for most patients with chronic respiratory disease are relatively similar during the 6MWT<sup>45</sup>, the use of SpO<sub>2</sub> nadir would be optimal absent the biases. Moreover, the definition of EID did not include the magnitude of SpO<sub>2</sub> decrease, however, only 33 of the patients with EID (7.5%) had a SpO<sub>2</sub> decline less than 4%. Third, blood gas analysis and diffusion capacity (DLCO) were not available in our dataset, which could provide further physiological evidence for the presence of EID. Despite these limitations, this study contributes with important information about emphysema, airflow limitation and obesity as determinants of EID and the use ADO index<sup>27</sup> as an additional clinical tool for screening EID in patients with COPD. Our findings may help clinicians to better understand the relationship of emphysema with EID and predict more accurately the EID.

## 5. Conclusions

In summary, EID occurs in about 20% of COPD patients. The severity of emphysema in moderate COPD increases EID in progressive manner. Several physiological determinants including presence of emphysema, severity of airflow limitation, impaired arterial oxygenation at rest and obesity, contribute to EID which seems to be captured by high ADO index values. Emphysematous patients with high ADO score should be monitored for EID upon embarking on a clinical exercise training program.

### **Conflict of interest**

None

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### Table Legends

**Table 1:** Values expressed as mean  $\pm$  SD; <sup>§</sup> One patients had a confirmed diagnosis for COPD but could not be assigned to a GOLD stage; <sup>§§</sup> in total 183 patient had undefined extent of emphysema (% valid percent); <sup>#</sup> Pearson Chi-Square. Significance level was set at P <0.05.

**Table 2:** Values expressed as mean  $\pm$  SD unless specified otherwise, <sup>#</sup> Pearson Chi-Square. Significance level was set at P <0.05.

**Table 3:** A multivariate-adjusted regression analysis; all the determinants (age, sex, BMI, FEV<sub>1</sub>, emphysema, and SpO<sub>2</sub> pre-walk) were included in the multivariate model. Significance level was set at P <0.05.

TABLES

Table 1. Baseline characteristics of COPD patients categorized by the prevalence of EID

Characteristics	All Subjects (n=2050)	Non-EID (n=1615, 79%)	EID (n=435, 21%)	P Value
Women, #, (%)	710 (35)	544 (34)	166 (38)	
Age, years	63.3 ± 7.1	63.1 ± 7.2	64.1 ± 6.8	0.012
BMI, kg/m <sup>2</sup>	26.5 ± 5.6	26.5 ± 5.5	26.7 ± 5.8	NS
Underweight	98 (5)	81 (5)	17 (4)	
Normal range	751 (37)	591 (36)	160 (37)	
Overweight	743 (36)	594 (37)	149 (34)	
Obese	458 (22)	349 (22)	109 (25)	NS <sup>#</sup>
FFMI, kg/m <sup>2</sup>	17.8 ± 3.4	17.8 ± 3.5	17.6 ± 3.4	NS
FEV <sub>1</sub> , % predicted	48.7 ± 15.7	51.2 ± 15.2	39.5 ± 13.9	<0.001
FVC, % predicted	80.0 ± 19.8	81.2 ± 19.2	75.4 ± 21.0	<0.001
FEV <sub>1</sub> /FVC, %	44.7 ± 11.4	46.2 ± 11.0	39.1 ± 11.1	<0.001
<i>GOLD Classification<sup>§</sup></i>				
Stage II	925 (45)	836 (52)	89 (20)	
Stage III	861 (42)	639 (39)	222 (51)	
Stage IV	263 (13)	139 (9)	124 (29)	<0.001 <sup>#</sup>
<i>Emphysema extent<sup>§§</sup></i>				
<5% [absent-trivial]	478 (26)	431 (30)	47 (11)	
5-25% [Mild]	406 (22)	356 (24)	50 (12)	
25-50% [Moderate]	361 (19)	293 (20)	68 (17)	
>50% [Severe-very severe]	622 (33)	375 (26)	247 (60)	<0.001 <sup>#</sup>
mMRC, Dyspnoea grade	1.7 ± 1.0	1.6 ± 1.0	2.0 ± 1.0	<0.001
≥2	1062 (53)	775 (48)	287 (66)	<0.001 <sup>#</sup>
SGRQ-C Total Score	47.8 ± 18.1	46.5 ± 18.5	52.6 ± 15.6	<0.001
≥50 points, n (%)	934 (47)	700 (43)	234 (54)	
Current Smokers, n (%)	742 (36)	639 (40)	103 (24)	<0.001 <sup>#</sup>

BMI: Body Mass Index, FFMI: Fat-Free Mass Index, FEV<sub>1</sub>: Force Expiratory Volume at 1 sec, FVC: Force Vital Capacity, mMRC: modified Medical Research Council Dyspnea Scale, SGRQ-C: St. George's Respiratory Questionnaire for COPD (40-item version)

Table 2. Six-Minute Walk Test characteristics and multi-dimensional indices categorized by the prevalence of EID

<i>Characteristics</i>	<b>All Subjects (n=2050)</b>	<b>Non-EID (n=1615, 79%)</b>	<b>EID (n=435, 21%)</b>	<b>P Value</b>
6MWD, m, $\pm$ SD	372 $\pm$ 121	382 $\pm$ 119	334 $\pm$ 12	<0.001
6MWD, % predicted	64 $\pm$ 21	66 $\pm$ 20	58 $\pm$ 21	<0.001
SpO <sub>2</sub> , % pre	94.7 $\pm$ 2.2	95.1 $\pm$ 2.0	93.1 $\pm$ 2.3	<0.001
SpO <sub>2</sub> , % post	91.8 $\pm$ 5.0	93.9 $\pm$ 2.6	84.1 $\pm$ 4.3	<0.001
$\Delta$ SpO <sub>2</sub> , %	-2.9 $\pm$ 4.3	-1.2 $\pm$ 2.4	-9.0 $\pm$ 4.8	<0.001
HR pre, b/m	82 $\pm$ 14	81 $\pm$ 14	85 $\pm$ 14	<0.001
HR post, b/m	100 $\pm$ 18	98 $\pm$ 17	108 $\pm$ 19	<0.001
$\Delta$ HR, b/m	18 $\pm$ 14	17 $\pm$ 13	23 $\pm$ 16	<0.001
<i>Borg Scale</i>				
Dyspnoea, pre	1.6 $\pm$ 1.8	1.5 $\pm$ 1.8	1.7 $\pm$ 1.9	NS
Dyspnoea, post	3.9 $\pm$ 2.4	3.6 $\pm$ 2.3	4.7 $\pm$ 2.3	<0.001
$\Delta$ Dyspnoea	2.3 $\pm$ 2.0	2.1 $\pm$ 1.9	3.0 $\pm$ 2.2	<0.001
Fatigue, pre	1.3 $\pm$ 1.8	1.3 $\pm$ 1.8	1.3 $\pm$ 1.8	NS
Fatigue, post	2.7 $\pm$ 2.5	2.6 $\pm$ 2.5	2.7 $\pm$ 2.5	NS
$\Delta$ Fatigue	1.4 $\pm$ 1.9	1.4 $\pm$ 1.8	1.4 $\pm$ 1.9	NS
ADO index, score	3.7 $\pm$ 1.5	3.5 $\pm$ 1.5	4.4 $\pm$ 1.4	<0.001
$\geq$ 6 points, n, (%)	245 (12)	148 (9)	97 (22)	<0.001 <sup>#</sup>
BODE index, score	3.1 $\pm$ 2.1	2.8 $\pm$ 2.0	4.2 $\pm$ 2.1	<0.001
$\geq$ 6 points, n, (%)	456 (22)	286 (18)	170 (39)	<0.001 <sup>#</sup>

6MWD: Six-min walk distance, SpO<sub>2</sub>: Oxygen saturation, HR: Heart rate, ADO index: "Age, Dyspnoea, and airflow Obstruction", BODE index: "Body-mass index, airflow Obstruction, Dyspnea, and Exercise", EID: Exercise-induced oxygen desaturation (SpO<sub>2</sub> post  $\leq$ 88%)

Table 3. Logistic regression: Determinants of EID in COPD patients

Determinants	Subjects n	EID n, (%)	Crude OR (95%CI)	P value	Adjust OR (95%CI)	P value
<b>Age</b>						
<60 years	594	106 (18)	1		1	
≥60 years	1456	329 (23)	1.34 (1.05-1.71)	0.017	1.21 (0.91-1.61)	NS
<b>Sex</b>						
Male	1340	269 (20)	1		1	
Female	710	166 (23)	1.22 (0.98-1.51)	NS	1.30 (1.00-1.68)	NS
<b>BMI</b>						
<30 kg/m <sup>2</sup>	1592	326 (20)	1		1	
≥30 kg/m <sup>2</sup>	458	109 (24)	1.21 (0.95-1.55)	NS	1.57 (1.15-2.14)	0.005
<b>FEV<sub>1</sub></b>						
>44%	1198	141 (12)	1		1	
≤44%	851	294 (35)	3.96 (3.16-4.96)	<0.001	3.14 (2.42-4.07)	<0.001
<b>Emphysema</b>						
Absent to mild	884	97 (11)	1		1	
Moderate to very severe	983	315 (32)	3.83 (2.98-4.91)	<0.001	3.37 (2.52-4.51)	<0.001
<b>SpO<sub>2</sub>% pre-walk</b>						
>93%	1506	194 (13)	1		1	
≤93%	544	241 (44)	5.38 (4.29-6.75)	<0.001	4.75 (3.69-6.13)	<0.001

BMI: Body Mass Index, FEV<sub>1</sub>: Force Expiratory Volume at 1 sec, SpO<sub>2</sub>: Oxygen saturation. Multivariate-adjusted model including all the determinants.

## Figure Legends

**Figure 1.** EID progressively increased across the GOLD stages in COPD. A total of 435 subjects (21%) in the ECLIPSE cohort exhibited EID.

**Figure 2.** Frequency distribution of post-walk SpO<sub>2</sub> and EID ( $\leq 88\%$ ) stratified by the GOLD stages and the degrees of QCT-emphysema. The dot line marks the threshold value for the presence of EID (SpO<sub>2</sub> post-walk  $\leq 88\%$ ).

**Figure 3.** A combination of certain lung function and baseline oxygen saturation characteristics for the prediction of EID revealed that the highest proportion of patients (81%) who exhibit EID are characterized by moderate to very severe emphysema (QCT score 3-5), obesity, impaired FEV<sub>1</sub> and low resting values of SpO<sub>2</sub> pre-walk.

**Online figure 1.** Comparisons of ADO index between EID and non-EID across the GOLD stages and the degrees of QCT-emphysema. Asterisks denotes significant difference (\*  $p < 0.05$ ; \*\*  $p < 0.001$ ).

Figure 01

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# Prevalence of EID

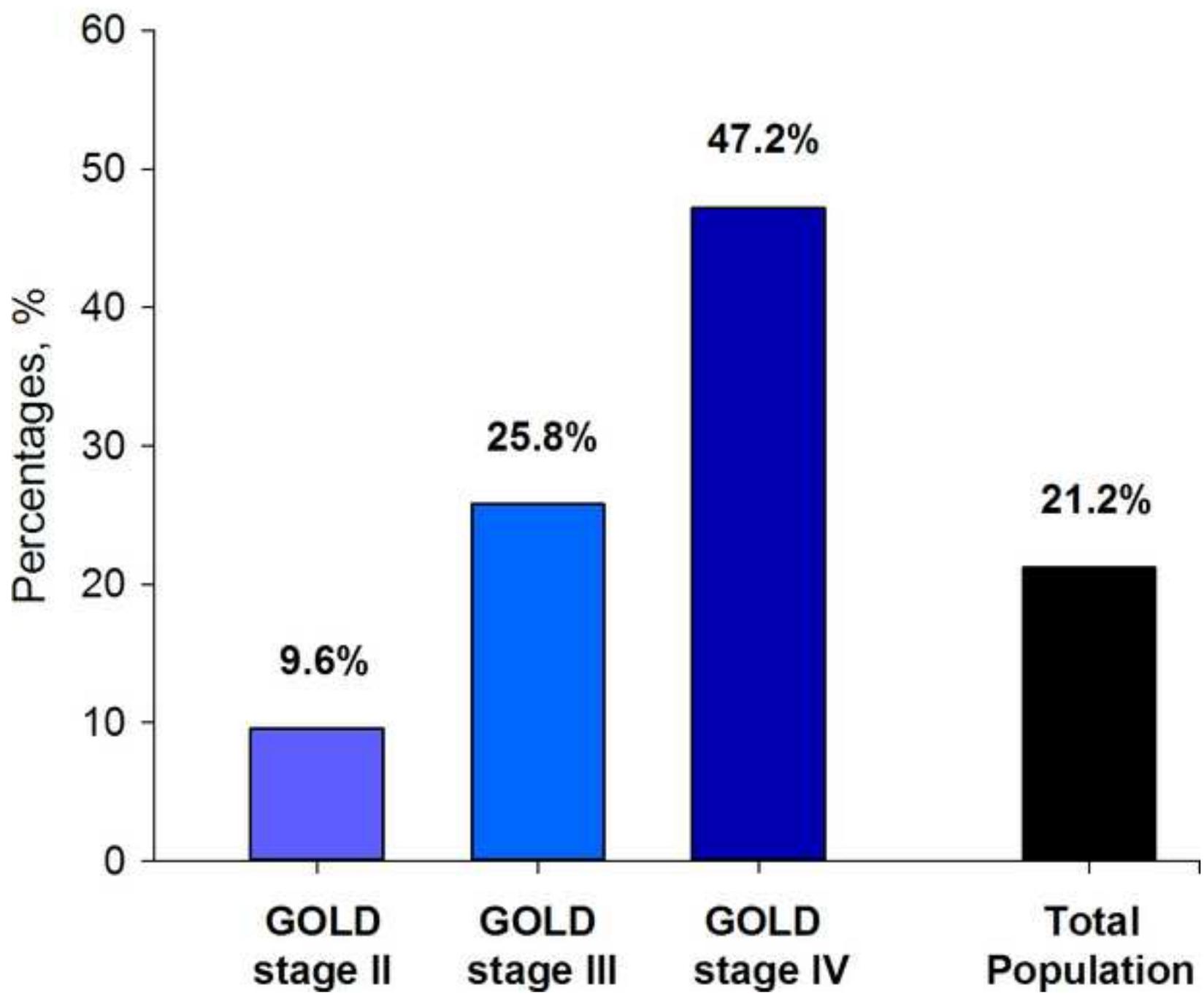


Figure 02

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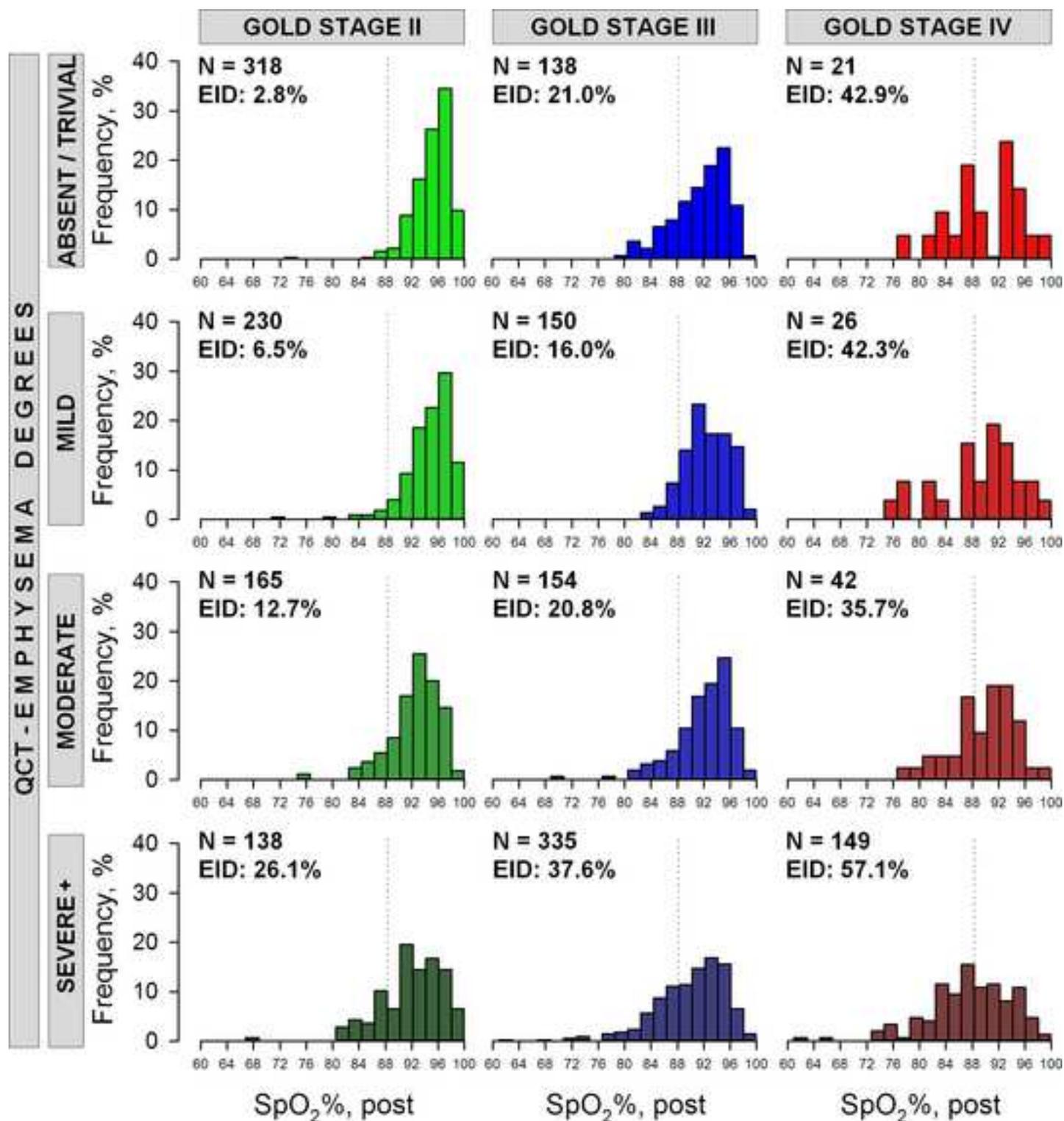
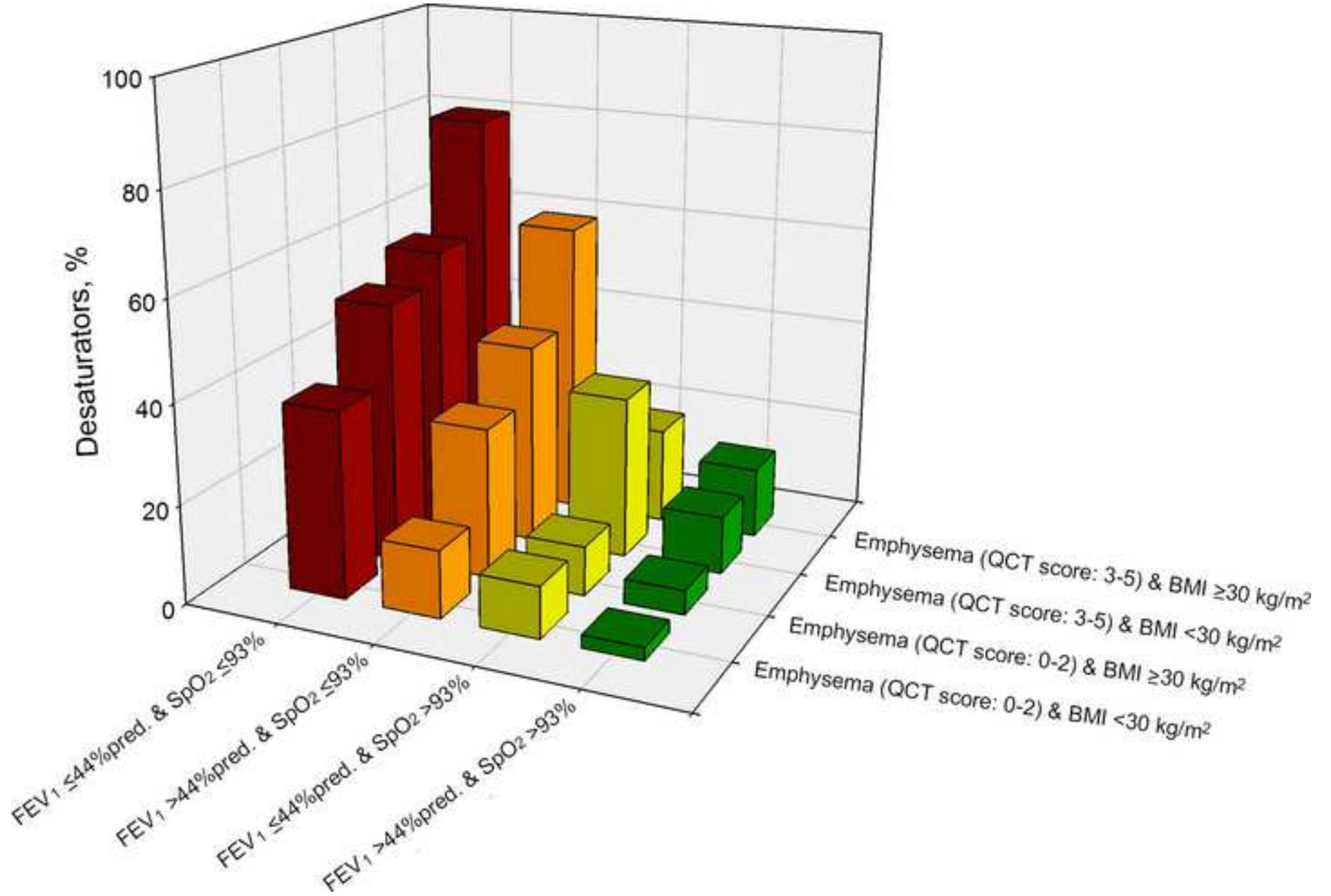
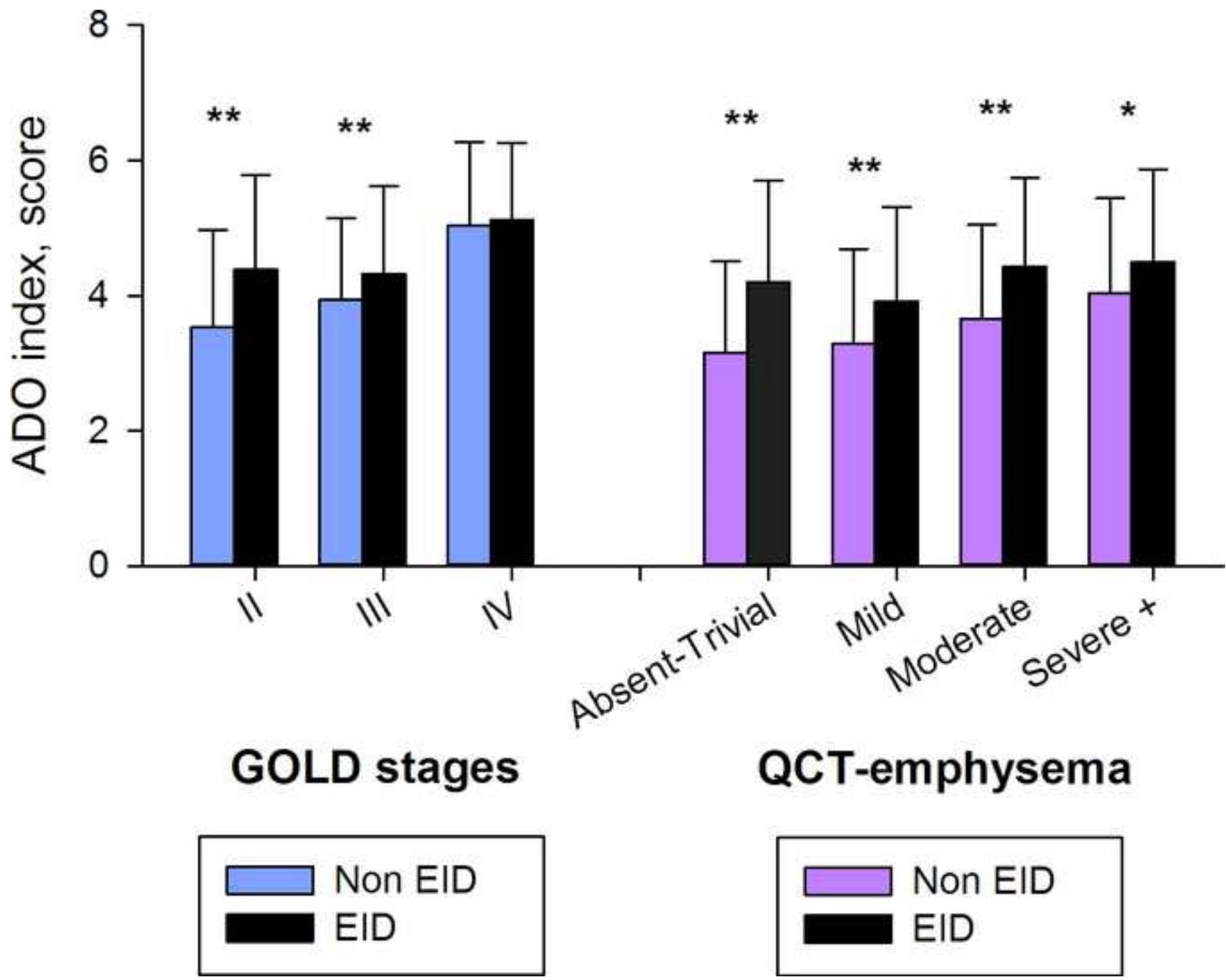


Figure 03  
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**Supplementary Data**

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