**CT-defined emphysema in COPD patients and risk for change in desaturation status in 6-minute walk test**

Marie Waatevik [1], Bente Frisk [2,3], Francisco Gómez Real [4,6], Jon Andrew Hardie [4], Per Bakke [4], Tomas Mikal Eagan [4,5], Ane Johannessen[7]

1. Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway
2. Dept of Health and Functioning, Western Norway University of Applied Sciences, Bergen, Norway
3. Dept of Physiotherapy, Haukeland University Hospital, Bergen, Norway
4. Dept of Clinical Science, University of Bergen, Bergen, Norway
5. Dept of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway
6. Dept of Gynecology and Obstetrics, Haukeland University Hospital, Bergen, Norway
7. Centre for International Health, Department of Global Public Health and Primary Care University of Bergen, Bergen, Norway

Corresponding author:
Marie Waatevik
Centre for clinical research
Haukeland University Hospital
5021 Bergen, Norway
Email: marie.waatevik@helse-bergen.no

**Conflict of interest statements**

M Waatevik, B Frisk, F Real, JA Hardie and A Johannessen have no conflict of interest to report.

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**Abbreviations**

AUC – area under the curve

BD – bronchodilator

CI – confidence interval

COPD – chronic obstructive pulmonary disease

CT – computed tomography

EID – exercise induced desaturation

$FEV_1$ - forced expiratory volume in one second

FVC – forced vital capacity

LAA –low attenuation areas

mMRC – modified medical research council

ROC – receiver operating curve

RR – relative risk

6MWT – 6 minute walk test

6MWD – 6 minute walk distance

**Key words:** Emphysema, COPD, 6MWT, exercise induced desaturation, $FEV_1$/lung function

**Abstract (word count: 244)**

**Background:** Emphysema and exercise induced desaturation (EID) are both related to poorer COPD prognosis. More knowledge of associations between emphysema and desaturation is needed for more efficient disease management.

**Research question**: Is emphysema a risk factor for both new and repeated desaturation, and is emphysema of more or less importance than other known risk factors?

**Methods:** 283 COPD patients completed a 6-minute walk test (6MWT) at baseline and one year later in the Bergen COPD cohort study 2006-2011. Degree of emphysema was assessed as percent of low attenuation areas under -950 Hounsfield units (%LAA) using high-resolution computed tomography at baseline.

We performed multinomial logistic regression analysis, receiver operating curves (ROC) and area under the curve (AUC) estimations. Dominance analysis was used to rank emphysema and risk factors in terms of importance.

**Results**: A one percent increase in %LAA increases the relative risk (RR) of new desaturation by 10% (RR 1.1 (95%CI 1.1, 1.2) and for repeated desaturation by 20% (RR 1.2 (95%CI 1.1, 1.3). Compared with other important desaturation risk factors, %LAA ranked as number one in the dominance analysis, accounting for 50% and 37% of the predicted variance for new and repeated desaturators, respectively. $FEV_1$ % predicted accounted for 9% and 24%, and resting $SpO_2$ accounted for 22% and 21% for new and repeated desaturation.

**Conclusion**: Emphysema increases the risk of developing and repeatedly experiencing EID. Emphysema seems to be a more important risk factor for desaturation than $FEV_1$% predicted and resting saturation.

**Introduction**

Exercise induced desaturation (EID) is shown to be present in a substantial portion of patients with chronic obstructive pulmonary disease (COPD) [1]. EID has shown to be a contributor to COPD prognosis as a risk factor for increased mortality, hospitalizations, decline in lung function and muscle mass, and increased number of exacerbations [2-5]. Desaturation itself is associated with airflow limitation, arterial oxygen saturation at rest and obesity.

Emphysema in COPD patients is associated with increased mortality [6], higher number of exacerbations [7], higher BODE score [8], dyspnea [9], and impairments in quality of life [10], also in patients without airflow limitations [11].

Emphysema in COPD patients have also shown a significant association with desaturation in the six minute walk test (6MWT) [4, 12-14], and Andrianopoulous et al [13] showed that a very low forced expiratory volume in one second ($FEV_1$) and severe emphysema might overlap in contribution on occurrence of desaturation.

However, although studies have looked at the linkage of emphysema measured with CT and exercise in COPD, to our knowledge no studies have looked at emphysema as a risk factor for the *development* of exercise-induced desaturation over time and investigated whether emphysema could be a risk factor for *new onset* of desaturation as well as *repeated* desaturation and whether emphysema is of more or less importance than other known risk factors. Since emphysema and desaturation are both related to poorer COPD prognosis, an increased knowledge of their relationship could be valuable in disease management, especially rehabilitation programs.

The aim of the study was to investigate whether computed tomography (CT) defined emphysema is a risk factor for change in desaturation status, and whether that association is of more importance than other known risk factors such as $FEV_1$ in % of predicted, resting oxygen saturation ($SpO_2$), rate of exacerbations and obesity.

## Methods

*Design and participants*

A flow chart of the study design is presented in figure 1. There were 433 COPD patients included in the Bergen COPD Cohort Study, a longitudinal prospective observation study from 2006-2010. All COPD patients were between 40-76 years old at inclusion, were ever smokers with >10 packyears, had post bronchodilator $FEV_1$ % predicted <80% and post bronchodilation (BD) $FEV_1$/forced vital capacity (FVC) ratio below 0.7. Selection of the participants have been described in detail previously [15]. At baseline, 371 patients completed a six-minute walk test (6MWT) and of those, 283 completed a new 6MWT one year later.

Informed and written consent was obtained from the participants prior to inclusion. The regional committee of medical research ethics (REK Vest, case number 165.08) approved the Bergen COPD Cohort Study. This study complies with the STROBE guidelines [16].

*Data collection*

Data was collected from clinical examinations, interviews by the study physician and self-administered questionnaires at baseline. 6MWT was also performed at follow-up one year later.

*Outcomes*

The 6MWT has previously been described in detail [1]. No practice test was done. Patients using oxygen supplementation or stopping before 6 minutes were excluded from the analysis (n=24). Additionally, patients who only desaturated in the first 6MWT were also excluded (n=12). $SpO_2$ was measured before and after each test using a wrist worn Nonin 3100 pulse oximeter with a finger sensor (Nonin Medical Inc., Plymouth, MN, USA). Desaturation was defined according to the Royal College of Physicians' guidelines as $\geq$4% reduction between arterial oxygen saturation measured by pulse oximetry pre- and post-test, and post-test $SpO_2$ <90% [17]. Desaturation status in the two

6MWTs was defined using three categories: no desaturation in both tests (non-desaturators), desaturation only at the second test (new desaturators) and desaturation at both tests (repeated desaturators).

*Exposures and covariates*

The main exposure in this study was CT-defined emphysema. Other exposures of interest were $FEV_1$ % predicted, resting $SpO_2$ and obesity. In addition, we considered a priori the following covariates for inclusion in the multivariate analyses: age, gender, smoking status, six-minute walk distance (6MWD), forced vital capacity (FVC) % predicted, Charlson comorbidity score, rate of exacerbations between baseline and follow-up, and modified Medical Research Council (mMRC) dyspnea score [18]. Covariates that showed no significant association with desaturation status in univariate analyses were left out of the multivariate model.

All patients underwent CT scans using GE Healthcare multidetector-row CT scanner. The scans were done in supine position at suspended full inspiration without administration of intravenous contrast. Exposure settings were 120 kVp and 40 mAs and images were reconstructed at 1.25 mm contiguous slices, using a low spatial frequency reconstruction algorithm (GE: Standard). The CT scans were analyzed using Pulmonary Workstation 2.0 software (VIDA Diagnostics, Iowa City, IA). Briefly, the lungs were segmented from the thorax wall, heart, and main pulmonary vessels, followed by segmentation of the individual lobes. The airways were segmented using a region-growing algorithm starting in the trachea and projecting to the smallest airway visible on the CT scan [19].

The extent of emphysema was estimated using the threshold technique, quantifying the percent of lung voxels with an apparent x-ray attenuation value below (% low attenuation areas, %LAA) -950 Hounsfield units (HU). This cut-off was chosen because it has previously been shown to be appropriate for the same CT acquisition technique as we have used in our study [20, 21].

$FEV_1$ and FVC were measured using a Viasys-Jaeger Masterscope (Viasys, Hoechberg, Germany) before and after inhalation of 0.4 mg salbutamol. We used Norwegian pre-BD reference values to calculate % predicted of $FEV_1$ and FVC [22].

Fat mass index (FMI) was assessed by body composition measurements using a Bodystat 1500 (Bodystat LTD, Isle of Man, England). FMI was calculated as fat mass divided by squared height ($kg \cdot m^{-2}$). Obesity was defined as FMI >13.5 $kg \cdot m^{-2}$ (females) and >9.3 $kg \cdot m^{-2}$ (males) [23].

Patients were categorized as current or ex-smokers based on their smoking history at baseline. Breathlessness was registered using mMRC dyspnea scale, a self-administered questionnaire, and we used a ≥2 score as cutoff. Charlson comorbidity score was calculated from the physician interview [24, 25]. 6MWD (meters) was measured after the patients had walked as far as possible for 6 minutes in the 6MWT. Information on number of exacerbations between baseline and follow-up was collected by the study physician and was dichotomized into having zero exacerbation or having 1 or more exacerbations in the year between baseline and follow-up.

*Statistical analyses*

All analyses were complete case analyses and performed using Stata 16 (StataCorp LP, College Station, TX, USA). P-values were two-sided and values <0.05 were considered statistically significant.

Since desaturation status was a multiple outcome, multinomial logistic regression with relative risk (RR) was used to examine the association between %LAA and desaturation status. The analysis was performed both univariate and after adjustment for covariates. As both outcomes are included in the same analysis, we adjusted for covariates if they were significant in univariate analysis for at least one of the outcome categories.

To examine how %LAA, $FEV_1$ % predicted, and resting $SpO_2$ predict the probability of desaturation, we used logistic regression analyses with post hoc Receiver operating curves (ROC) for differentiation

of desaturators and non-desaturators, and with areas under the curve (AUC) estimations to assess diagnostic performance. An AUC of 1 indicates a perfect classification with 100% sensitivity and 100% specificity, and an AUC of 0.5 means no discriminating value. In these analyses, desaturation status was treated as two binary outcomes; new desaturators vs non-desaturators and repeated desaturators vs non-desaturators. This analysis was not done for obesity due to it being a categorical variable.

Multivariate dominance analysis was used to rank the exposures and covariates in terms of importance. This analysis examines the contribution of each predictor to the model's fit in all possible subset models and compare a weighted average $R^2$ in a pairwise fashion to the corresponding contributions of each of the other predictors [26]. The vector of standardized general dominance statistics was reported for each variable, summing up to 100% for all variables in the original multivariate model. These analyses were done separately for new desaturation and for repeated desaturation.

**Results**

The characteristics of the population are shown in table 1. In the first 6MWT, 20% desaturated, and 30% in the second test. Of those, 13% desaturated only in the second test, and 17% in both tests. Mean age was approximately 63 years in all desaturation groups, and there were 40% women overall. Median %LAA was highest among repeated desaturators, followed by new desaturators. The same pattern was seen for $FEV_1$ % predicted and resting $SpO_2$, the lowest values were seen in repeated desaturators and second lowest in new desaturators.

The univariate and multivariate multinomial logistic regression analyses with relative risks are shown in table 2 and 3. A one unit increase in %LAA was significantly associated with a 10% higher risk (RR 1.1 (95%CI 1.1, 1.2) of desaturating in the 6MWT one year later compared to not desaturating, and with a 20% higher risk (RR 1.2 (95%CI 1.1, 1.3) of desaturating in both 6MWTs. A 10% reduction in

$FEV_1$ % predicted was not significantly associated with being a new desaturator at follow-up but doubled the risk of repeated desaturation (RR 2.1 (95% CI 1.2, 3.4). For $SpO_2$, a one-unit decrease was associated with a 30 % higher risk (RR 1.3 (95%CI 1.1, 1.6) of desaturating one year later, and a 50% higher risk (RR 1.5 (95%CI 1.2, 1.8) of desaturating in both 6MWTs. There were no significant association between obesity and EID in either crude or adjusted analyses. Rate of exacerbations between baseline and follow-up was significantly associated with repeated desaturation in crude analyses. When included in the multivariate model, the association did not remain significant.

The ROC curves with AUC for new desaturators and repeated desaturators, and the predictive ability of the risk factors are shown in figure 2. %LAA showed good predictive ability (AUC=0.77) for new desaturators compared to non-desaturators. $FEV_1$ % predicted showed a lower predictive ability (AUC = 0.66) and the same was shown for resting $SpO_2$ (AUC = 0.60). %LAA also showed good predictive ability (AUC = 0.86) for repeated desaturation compared to non-desaturation, the same was shown for $FEV_1$ % (AUC = 0.84) and a slightly lower predictive ability for resting $SpO_2$ (AUC = 0.74).

The multivariate dominance analysis is presented in table 4. CT defined emphysema accounted for 50% and 37% of the predicted variance in new and repeated desaturation, respectively, and is ranked as number one for both desaturation statuses. $FEV_1$% predicted accounted for 9% and 24%, and resting $SpO_2$ accounted for 22% and 21% of the predicted variance for new and repeated desaturation. Obesity accounted for 2% and 1% respectively.

**Discussion**

This study of 283 COPD patients who completed two 6MWTs one year apart, shows that CT defined emphysema is an important risk factor for change in desaturation status in the 6MWT, even more important than $FEV_1$ % predicted and resting $SpO_2$. A one percent increase in %LAA increases the risk

of new desaturation by 10% and for repeated desaturation by 20%. Compared with other important desaturation risk factors, %LAA ranked as number one in the dominance analysis, accounting for 50% and 37% of the predicted variance for new and repeated desaturators, respectively.

COPD patients experience chronic airway limitation caused by small airway disease and emphysema. Emphysema involves destruction of the gas exchanging surfaces and the elastic recoil of the lung [27]. Impaired gas exchange can lead to mismatch between ventilation and perfusion (V/Q), which is seen as the major factor causing EID, but also reduced mixed venous oxygen tension may play an important role [28]. The relationship between emphysema and EID was first shown in a small study by Taugchi et al [12], and later in larger studies with more strength. Kim et al [4] analyzed 224 COPD patients and found that a CT emphysema index was independently associated with EID. Adrianopoulos and colleagues [13] investigated 2050 COPD patients in the large ECLIPSE study and found that emphysema was associated with EID, and together with obesity, severe airflow limitation and low resting $SpO_2$ could have a predictive value. The study by Ostridge et al [14] included 122 COPD patients and found that only %LAA independently predicted whether a patient desaturated or not.

The results concerning emphysema in this study are consistent with the other studies, but expands the knowledge of emphysema as a risk factor for change in desaturation status, and to our knowledge it is the first to investigate its relative importance compared to other known risk factors.

The studies by Kim et al [4], and Ostridge and colleagues [14] did not find a significant association between $FEV_1$ and desaturation in multivariate analyses. In the study by Adrianopoulos et al [13] they found that both emphysema and severe airflow limitation contributed to EID. In the current study we elaborate further on the knowledge from the work of Adrianopoulos et al [13], focusing on windows in disease progression through assessing separately whether emphysema was related to new desaturation or repeated desaturation, and investigating the relative importance of known risk factors. We found that lung function contributes to a much less degree than emphysema, particularly

to new onset of desaturation. $FEV_1$ % predicted was not significantly associated with EID in the new desaturation group and ranked as only the fourth most important risk factor in our model. This finding suggests that although new desaturators have had a decline in lung function, this decline is not steep enough to be predictive of EID. This is in line with Adrianopoulos et al [13] who found a $FEV_1$% predicted cutoff at 44% to be a determinant of EID. For the repeated desaturation group, where $FEV_1$ % predicted is 10% lower, it significantly associated with EID and ranked as the second most important variable in the model. Interestingly, the median %LAA is not very high in either group, which could mean that even mild to moderate emphysema is enough to impact development of EID.

Resting $SpO_2$ is a known predictor of EID, and our results are in line with other studies. In our analyses resting $SpO_2$ have a slightly lower AUC than $FEV_1$ % predicted in the ROC analyses for new desaturators, but were significantly associated with new desaturation in the multinomial logistic analyses and had a higher predicted variance in the dominance analyses. This is due to the fact that the ROC analyses are crude while the multinomial regression and dominance analysis adjust for other risk factors. It is plausible that resting $SpO_2$ has a more important role than $FEV_1$ % predicted in the stage of disease progression where EID materialize for the first time. However, as shown in the multivariate analyses of repeated desaturation, when $FEV_1$ declines further, its importance increases beyond resting $SpO_2$.

In this study we did not find a significant association between obesity and EID, either in crude or multivariate analyses. Upon a closer inspection of the multivariate analyses, we found that the association between obesity and EID was significant until adding mMRC to the model. It is likely that the association between obesity and EID was in fact partly caused by dyspnea, with obese subjects faster experiencing breathlessness than non-obese subjects. In the study by Adrianopoulos et al [13] they only found the association between obesity and EID significant in the multivariate analyses, suggesting that this relationship is only relevant when occurring together with other risk factors, and

mMRC was not included in their model. Ostridge et al [14] found no significant association between BMI and desaturation >5%, but BMI was treated as a linear variable and obesity was not specifically considered. Garcia-Talavera et al [29] found only a relationship between obesity and those who desaturated within the first minute, but they did not include measurements of emphysema. However, because of the different methodology in these studies and ours, they are not completely comparable, and together with a smaller population in our study, we would be cautious to conclude based on this analysis only.

This study includes both men and women with moderate to very severe COPD. As such, the results are not generalizable to all COPD patients, but they are applicable to COPD patients with clinically significant disease stages.

We analyzed the exposures prior in time to onset of desaturation, decreasing the risk of reverse causation, which is a strength of the study. The differentiation between new and repeated desaturation status is another strength, making it possible to analyze whether there are different risk factors for these patients. A third strength is using dominance analysis to determine the relative importance of the exposures as risk factors for new and repeated desaturation.

There are some limitations to this study. First, there were too few patients with more pronounced emphysema to analyse the effect of increasing emphysema severity on desaturation. A descriptive analysis using the same categories as in the study by Andrianoupolus [13] showed that most of the EID patients in our population had mild emphysema (%LAA 5-25%). A focus on emphysema severity could have strengthened our results and given more information on the relationship between emphysema and change in desaturation status. This would be important to address in a future study.

Second, we did not have information on $D_LCO$ at baseline. $D_LCO$ has also shown to be a determinant of EID [30, 31], and inclusion of $D_LCO$ in our model would have strengthened the analyses. A study by Saure et al [32] showed that when $D_LCO$ was added to the model, the significant association between emphysema and hypoxemia at rest disappeared. However, $D_LCO$ and emphysema are also closely

related, a higher degree of emphysema is associated with an impaired diffusion capacity [9] and with risk of collinearity if both are included in the same analyses. The study by Kim et al [4] decided to not include $D_LCO$ in their models due to this factor.

Third, we did not have information on nadir $SpO_2$. Studies has shown that desaturation within the first minute of 6MWT is a risk factor for developing hypoxemic respiratory failure and a higher probability of experiencing desaturation in daily activities [33, 34]. It is also shown that obesity and overweight are determinants of early desaturation [29], and it would have been interesting to know whether emphysema is a risk factor as well.

Fourth, the extent of emphysema was estimated using the threshold technique, quantifying the percent of lung voxels with an x-ray attenuation value below -950 HU. One could argue that this threshold may not be optimal and that values below this threshold indicate a reduced lung density due to the large amount of air with respect to lung tissue. Usually calculated at full inspiration, it can be measured also at full expiration with another threshold: -910 HU. However, a study by Wang and co-workers [35] investigated this further, quantifying emphysema using a density mask and testing a wide range of thresholds from −850 to −1000 HU. They found that despite variations in the optimal cut-off thresholds for individual lobes, the single threshold of −950 HU is still an acceptable threshold for density-based emphysema quantification.

Fifth, the CT scans were not spirometrically gated, and level of inspiration during the scan was thereby not controlled for [36]. This could be a potential bias as this could reduce the %LAA.

That CT defined emphysema is an important risk factor for change in desaturation status among moderate to severe COPD patients, does of course not mean that all COPD patients should undergo CT examinations to assess risk for desaturation. This would be both costly and invasive. However, in this patient group, a large proportion will have CT examinations regardless – either as part of disease monitoring or because of comorbidities. For this proportion, it would be very valuable to also use the information from the CT examinations to determine their risk for desaturation. Together, this will

enable health professionals to better predict patients' prognosis, and to better tailor future disease management.

**Conclusion**

This study has shown that emphysema increases the risk of developing and repeatedly experiencing EID, and that emphysema seems to be a more important risk factor for desaturation than $FEV_1$% predicted and resting saturation. These results add knowledge to what increases the risk of developing EID, and monitoring EID in COPD patients with known emphysema should be encouraged.

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**Table 1. Baseline characteristics of the 283 COPD patients in the Bergen COPD Cohort Study**

| | All patients | No desaturation 6MWT1 and 6MWT2 | New desaturators 6MWT2 | Repeated desaturators 6MWT1 and 6MWT2 | p-value |
|---|---|---|---|---|---|
| | 283 | 198 | 37 | 48 | |
| Age, mean (SD) | 63.2 (6.4) | 63.1 (6.6) | 63.3 (5.5) | 63.7 (6.1) | 0.82 |
| Gender, n (%) | | | | | 0.93 |
| women | 112 (40%) | 78 (39%) | 14 (38%) | 20 (42%) | |
| men | 171 (60%) | 120 (61%) | 23 (62%) | 28 (58%) | |
| Smoking status, n (%) | | | | | 0.002 |
| Ex | 158 (56%) | 97 (49%) | 27 (73%) | 34 (71%) | |
| Current | 125 (44%) | 101 (51%) | 10 (27%) | 14 (29%) | |
| $FEV_1$ %, mean (SD) | 51.3 (13) | 54.9 (12.2) | 48.0 (12.1) | 38.9 (9.8) | <0.001 |
| FVC %, mean (SD) | 87.6 (15) | 87.6 (14.8) | 91.5 (15.6) | 84.7 (16.1) | 0.12 |
| mMRC dyspnea scale[1], n (%) | | | | | <0.001 |
| < 2 | 147 (57%) | 115 (65%) | 19 (52.8%) | 13 (28.9%) | |
| ≥ 2 | 111 (43%) | 62 (35%) | 17 (47.2%) | 32 (71.1%) | |
| Charlson comorbidity score, n (%) | | | | | 0.44 |
| 1 | 169 (60%) | 117 (59%) | 22 (59%) | 30 (63%) | |
| 2 | 65 (23%) | 43 (22%) | 8 (22%) | 14 (29%) | |
| ≥3 | 49 (17%) | 38 (19%) | 7 (19%) | 4 (8%) | |
| Body composition[2], n (%) | | | | | 0.70 |
| no obesity | 242 (85%) | 171 (86%) | 30 (81%) | 41 (85%) | |
| obesity | 41 (15%) | 27 (14%) | 7 (19%) | 7 (15%) | |
| Exacerbation rate during 1yr follow-up, n (%) | | | | | |
| <1 | 174 (62%) | 132 (67%) | 21 (57%) | 21 (44%) | 0.01 |
| ≥1 | 109 (39%) | 66 (33%) | 16 (43%) | 27 (56%) | |
| %LAA, median | 8.9 (4.5, 17.0) | 6.3 (3.5, 12.1) | 12.6 (9.1, 19.7) | 21.7 (13.8, 26.9) | <0.001 |
| 6MWD baseline, m (SD) | 444.9 (93.0) | 450.9 (93.8) | 432.1 (84.8) | 430.0 (94.6) | 0.25 |
| $SpO_2$ pre 6MWT1, mean (SD) | 94.5 (2.5) | 95.0 (2.1) | 93.8 (3.5) | 93.0 (2.4) | <0.001 |

$FEV_1$ = forced expiratory volume in one second, mMRC = modified medical research council, %LAA= % low attenuation areas, 6MWD = 6 minute walk distance

[1]Missing mMRC values n=21

[2]Body composition assessed by Fat Mass Index (FMI) calculation. Obesity was defined as FMI >13.5 $kg \cdot m^{-2}$ (females) and >9.3 $kg \cdot m^{-2}$ (males)

**Table 2. Univariate multinomial logistic regression analysis of associations between desaturation status, exposures and covariates**

| | New desaturator | | | Repeated desaturator | | |
|---|---|---|---|---|---|---|
| | **RR** | **95% CI** | **p-value** | **RR** | **95% CI** | **p-value** |
| %LAA | 1.1 | 1.1, 1.2 | **<0.001** | 1.2 | 1.1, 1.2 | **<0.001** |
| $FEV_1$ %[1] | 1.6 | 1.2, 2.1 | **0.002** | 3.2 | 2.3, 4.5 | **<0.001** |
| Resting $SpO_2$[2] | 1.3 | 1.1, 1,4 | **0.002** | 1,4 | 1.2, 1.6 | **<0.001** |
| Body composition[3] | | | | | | |
| Obese | 1.5 | 0.6, 3.7 | 0.40 | 1.1 | 0.4, 2.7 | 0.87 |
| Age | 1.0 | 0.9, 1.1 | 0.82 | 1.0 | 0.9, 1.1 | 0.54 |
| Gender | 1.1 | 0.5, 2.2 | 0.86 | 0.9 | 0.5, 1.7 | 0.77 |
| 6MWD baseline | 1.0 | 0.99, 1.0 | 0.26 | 1.0 | 0.99, 1.0 | 0.16 |
| Smoking status | | | | | | |
| ex smokers | 0.4 | 0.2, 0.8 | **0.009** | 0.4 | 0.2, 0.8 | **0.008** |
| FVC %[1] | 0.8 | 0.7, 1.1 | 0.15 | 1.1 | 0.9, 1.4 | 0.23 |
| Charlson comorbidity score | | | | | | |
| 2 | 1.0 | 0.4, 2.4 | 0.98 | 1.2 | 0.6, 2.6 | 0.51 |
| 3 | 1.0 | 0.4, 2.5 | 0.96 | 0.4 | 0.1, 1.2 | 0.11 |
| mMRC[4] | | | | | | |
| ≥2 | 1.6 | 0.8,3.4 | 0.17 | 4.6 | 2.2, 9.3 | **<0.001** |
| ≥1 exacerbation rate during 1yr follow-up | 1.5 | 0.7, 3.1 | 0.25 | 2.6 | 1.3, 4.9 | **0.004** |

$FEV_1$ = forced expiratory volume in one second, mMRC = modified medical research council, %LAA= % low attenuation areas, 6MWD = 6 minute walk distance.

Reference categories: non-obese, current smokers, charlson score 1, mMRC score <2, <1 exacerbations

[1] RR per 10% decrease

[2]measured before the 6MWT at baseline, RR per % decrease

[3] Body composition assessed by Fat Mass Index (FMI) calculation. Obesity was defined as FMI >13.5 kg·m−2 (females) and >9.3 kg·m−2 (males).

[4]Missing mMRC values n=21

**Table 3. Multivariate multinomial logistic regression analysis of association between desaturation status and CT-defined emphysema in COPD patients, adjusted for other known risk factors and covariates**

| | New desaturation | | | Repeated desaturation | | |
|---|---|---|---|---|---|---|
| | **RR** | **95% CI** | **p-value** | **RR** | **95% CI** | **p-value** |
| %LAA | 1.1 | 1.1, 1.2 | **<0.001** | 1.2 | 1.1, 1.3 | **<0.001** |
| $FEV_1$ %[1] | 1.1 | 0.8, 1.7 | 0.56 | 2.1 | 1.3, 3.4 | **0.004** |
| Resting $SpO_2$[2] | 1.3 | 1.1, 1.6 | **0.002** | 1.5 | 1.2, 1.8 | **<0.001** |
| Obesity[3] | 1.9 | 0.6, 6.0 | 0.27 | 2.9 | 0.8, 10.7 | 0.10 |
| Age | 0.97 | 0.9, 1.0 | 0.37 | 1.0 | 0.9, 1.0 | 0.24 |
| Gender | 0.7 | 0.3, 1.6 | 0.36 | 0.4 | 0.2, 1.1 | 0.07 |
| Smoking status | | | | | | |
| ex smokers | 0.6 | 0.2, 1.4 | 0.20 | 0.7 | 0.3, 2.1 | 0.56 |
| mMRC[4] | | | | | | |
| ≥2 | 1.0 | 0.4, 2.4 | 0.97 | 1.7 | 0.6, 4.5 | 0.29 |
| ≥1 exacerbation rate during 1yr follow-up | 1.2 | 0.5, 2.8 | 0.64 | 1.9 | 0.8, 4.8 | 0.15 |

$FEV_1$ = forced expiratory volume in one second, mMRC = modified medical research council, %LAA= % low attenuation areas, 6MWD = 6 minute walk distance

Reference categories: non-obese, current smokers, mMRC score <2, <1 exacerbations

[1] RR per 10% decrease

[2]measured before the 6MWT at baseline, RR per % decrease

[3]Obesity was defined as FMI >13.5 kg·m−2 (females) and >9.3 kg·m−2 (males)

[4]Missing mMRC values n=21

**Table 4. Multivariate dominance analysis of the relative importance of the risk factors for new and repeated EID in the 6MWT of COPD patients**

| | New desaturation | | Repeated desaturation | |
|---|---|---|---|---|
| Variables | **Standardized domin stat** | **Rank** | **Standardized domin stat** | **Rank** |
| % LAA | 0.50 | 1 | 0.37 | 1 |
| $FEV_1$ %[1] | 0.09 | 4 | 0.24 | 2 |
| Resting $SpO_2$[2] | 0.22 | 2 | 0.21 | 3 |
| mMRC[3] | 0.01 | 7 | 0.06 | 4 |
| Exacerbation rate | 0.02 | 6 | 0.04 | 5 |
| Smoking status | 0.12 | 3 | 0.03 | 6 |
| Gender | 0.01 | 8 | 0.02 | 7 |
| Obesity[4] | 0.02 | 5 | 0.01 | 8 |
| Age | 0.01 | 9 | 0.01 | 9 |

$FEV_1$ = forced expiratory volume in one second, mMRC = modified medical research council, %LAA= % low attenuation areas, 6MWD = 6 minute walk distance

[1] Per 10% decrease

[2]measured before the 6MWT at baseline

[3]Obesity was defined as FMI >13.5 kg·m−2 (females) and >9.3 kg·m−2 (males)

[4]Missing mMRC values n=21

**Figure legends**

**Figure 1. Flow chart of the study design and the COPD patients who performed 6MWT and underwent HRCT at baseline and at follow-up one year later in the Bergen COPD Cohort Study.**

**Figure 2. ROC curves with Area Under the Curve of the risk factors; %LAA, $FEV_1$% predicted and resting $SpO_2$ for new and repeated desaturation**