# COPD comorbidities predict high mortality – asthma-COPD-overlap has better prognosis

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# COPD comorbidities predict high mortality – asthma-COPD-overlap has better prognosis

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## Abstract

The purpose of this study was to investigate the characteristics and survival of patients with COPD and asthma-COPD overlap (ACO) and how these patient groups differ from each other. We examined the impact of different comorbidities, multimorbidity, lung function and other factors have on survival in ~~non-asthmatic~~ COPD and ACO patients. We also examined the causes of death to determine how many patients die of other than respiratory diseases.

This retrospective study includes 214 patients with an exacerbation of COPD requiring hospitalisation during the year of 2005. The patients were followed up until the end of year 2015. The survival of ACO patients was significantly higher than ~~non-asthmatic~~ COPD patients (4,7 vs 1,7 years, p= 0,001). Poor lung function predicted worse survival in both patient groups, but the prognosis was still better in ACO patients with both FEV1 over and under 50 % of predicted (median survival ~~(~~8,4 years vs. 5,8 years P<0.001). compared to COPD (4.9 and 3.1 years, respectively).~~When taking lung function in account, prognosis was better only in the ACO group with FEV1 over or under 50 % of predicted (8,4 years vs. 5,8 years P<0.001).~~ In this study setting, the negative effect of having three or more comorbidities on survival was significant in both groups. We didn't see major differences in the profiles of comorbidity patterns, in the underlying cause of deaths or in the pulmonary functions between ACO and COPD groups at the beginning of follow-up. Patients with a BMI over 25 seemed to have a trend for better survival (p = 0.055), but no differences were found between ACO and COPD groups.

## Introduction

Asthma-COPD Overlap (ACO) is a relatively new phenotype of chronic obstructive pulmonary disease and was added to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) ~~Guidelines~~ in year 2015 [1]. ACO is characterized as chronic, incompletely reversible airflow limitation with several clinical features associated with asthma and others with COPD. However, there has not yet been enough evidence to determine a specific definition for the syndrome or to define disease pathogenesis or the optimal treatment [2]. ACO is not a single disease, instead it represents overlap of both disorders and includes patients with different phenotypes of both diagnoses [2].

The prevalence of ACO ranges in different studies from 15% to 55%, with variation by age and ~~gender~~sex [1-3]. A Finnish study examining hospital discharge data from the National Institute of Health and Welfare found that 16.1% of patients hospitalised with an exacerbation of asthma or COPD also had an overlap of these diagnoses [4]. Research has suggested that asthma and COPD overlap particularly in smokers and elderly patients [2], though some studies have found that the patients suffering from both asthma and COPD are more often younger, female, have higher BMI and a higher burden of comorbidities than when comparing ACO with asthma and COPD [5]. Patients with ACO have also been shown to have worse outcomes than patients with asthma or COPD alone [2] and to experience exacerbations more frequently, have a more rapid decline in lung function, to consume more healthcare resources and to have higher mortality than patients without overlap. [1,2,6]

Exacerbations are defined as acute and sustained worsening of COPD symptoms, apart from day-to-day variation, leading to change in medication and / or hospitalisation [7]. Frequent acute exacerbations and hospitalisation for exacerbations have been shown to have a negative impact on the prognosis of COPD patients [8,9].

The aim of this study was to look at the prognosis of severe exacerbating COPD and find out, whether the prognosis and comorbidity profile of asthma-COPD-phenotype differs from non-asthma phenotype. We also investigated the prevalence and incidence of comorbidities in COPD and ACO patients and evaluated their effect on survival in a Finnish population. In the light of previous studies, comorbidities in COPD are frequent and influence negatively on survival [10] and ACO patients seem to have a higher burden of comorbidities [11].

## Methods

This study was a retrospective hospital register based study that consists of patients with COPD treated in Oulu University Hospital during the year 2005. The patients for the cohort were chosen from the hospital register based on the diagnosis number (International Classification of Diseases, COPD ICD 10: J41-J44). For statistical analysis, patients were divided into two groups: COPD patients with asthma-COPD overlap (from now on referred to as ACO patients) and COPD patients without an asthmatic component present (COPD patients). The presence of asthma was determined by doctor-diagnosed asthma documented in patient records of Oulu University Hospital and/or listed in the diagnoses of hospital treatment episode(s) or out-patient visit. Patient characteristics were collected from the patient files of Oulu University Hospital until the end of 2015, with retrospective follow-up of patients ~~up to~~ maximum of 10 full years. Besides, all the death certificates were collected from the data archive and inspected regarding the cause of death as well as the exact day of death.

The material which consisted of a total of 214 patients were analysed with statistical software SPSS Statistics. We divided the patients into two groups, COPD patients with asthma component (ACO) and the patients with diagnosis of COPD without the asthmatic features. All the frequencies between the groups were calculated by the statistical programme whereas significance between the two groups were determined by the evaluation of t-test and Mann-Whitney U -test depending on the distribution of a chosen parameter within the groups. The survival was examined by Kaplan-Meier survival test and the curves were formed by the programme. Evaluation of significance were considered by the Log-rank test which defined the significance pair wisely over the strata in the graphics. Moreover, Chi-square test was used to analyse the difference between ACO and COPD -groups in the crosstabs.

The study plan was approved by the Regional Ethics Committee of the Northern Ostrobothnia Hospital District. The patients were not contacted regarding this study. The ethical principles of medical research according to Helsinki declaration have been followed.

## Results

### *Patient characteristics*

The patients in ACO group were younger (67 years vs 70 years, $p< 0.05$), more often female (34% in ACO group% vs. 22% in COPD group) and more often overweight (BMI 29 vs 27, $p<0.05$) compared to COPD patients. Among all the patients in the study, ~~O~~only 2.3% ~~of all patients~~ were known to be lifelong non-smokers and all these patients had ACO. 49% were current smokers and 49% ex-smokers. ~~there was~~ There was no statistically significant difference in current smoking status of ACO and COPD patients, but ~~an equal amount of current and ex-smokers (49% of each). Only 2.3% of all patients were known to be lifelong non-smokers and all~~

these patients had ACO. There was no statistically significant difference in current smoking status of ACO and COPD patients, but COPD patients had more pack years compared to ACO patients (44 pack years vs. 39 pack years, p = 0.05). There was no difference in lung function measured by forced expiratory volume in the first second (FEV1) or diffusing capacity of carbon dioxide (corrected for haemoglobin, DLCOc) between the two patient groups. Patient characteristics are described in table 1.

***Prevalence of comorbidities***

There was no significant difference in the number of comorbidities and both patient groups had a median of three diagnosed comorbidities at the time of index hospitalisation in year 2005. Lung cancer was more often diagnosed in the COPD groups before the follow-up (Table 2).

***Survival and lung function***

The survival of ACO patients was significantly better than of non-asthmatic COPD patients (4,7 vs 1,7 years, p= 0,001) (Figure 1.). The lung function data was available only in 84/128 cases in ACO group and in 38/86 in COPD group. In cases with lung function data available, Ppoor lung function predicted worse survival in both patient groups (Figure 2), but the prognosis was still better in ACO patients with both FEV1 over and under 50 % of predicted. Median survival was 8.4 years for ACO patients with FEV1 >50 % predicted and 5.8 years for the patients with ACO with FEV1 <50% predicted, when in the COPD group median survival was 4.9 years for COPD with FEV1 >50% predicted and 3.1 for COPD with FEV1 <50% predicted ($p < 0.001$). The difference between ACO patients with under (N=20) and over 50% (N=46) of FEV1 % predicted remains ($p<0.01$) after excluding those patients who didn't meet the criteria for COPD (FEV1% < 70.0% after bronchodilator) in the spirometry done around the index year (± 2 years) but were diagnosed with COPD before.

***Survival and comorbidities***

The number of diagnosed comorbidities at the time of index COPD hospitalisation predicted survival. For patients with ACO and 0 to 2 comorbidities, the median survival was 6.0 years (N= 48) and for ACO patients with 3 or more than 3 comorbidities the survival was 3.7 years (N=81). For COPD patients with 0 to 2 comorbidities, the median survival was 2.4 years (N=42) and for COPD patients with 3 or more than 3 comorbidities 1.1 years (N=43). $P < 0.001$ (Figure 3).

Obese patients had a trend for better survival compared to non-obese patients with median survival for BMI < 25 3.3 years, and for BMI>25 5.7 years, p = 0.055), but the difference was not statistically significant (Figure 4). The number of underweight cases was very low (8 in COPD group and 3 in ACO group) and no differences between underweight cases compared to normal weight or obese patients could be calculated.

Survival between groups has been compared after excluding patients with lung cancer. These patients were more frequent at index date in COPD compared to ACO and may be the cause of the reduced survival. After exclusion of these cases, the results of survival analysis did not change remarkably and the median survival in COPD group after exclusion of lung cancer cases was 2,1 years, in ACO 4,6 years (p<0,001).

***Causes of death***

There were no differences in the underlying cause of deaths between ACO or COPD group (Table 3). The most common underlying cause of death was a disease of the respiratory system (ICD 10: J00-J99) in both ACO and COPD groups. The other recurring causes were diseases of the circulatory system (ICD 10: I00-I99) and neoplasms (ICD 10: C00-D49). "Other" causes included for example accidents, intoxications, complications of diabetes and gastrointestinal catastrophes. ~~These findings were similar to previous findings, where causes of death of COPD patients have been respiratory in 35-57%, cardiovascular in 25-27% and cancer in 20-33% of the cases [12-14].~~

## Discussion

In this study we found that patients with asthma-COPD-overlap have better prognosis compared to ~~non-asthmatic~~ COPD patients and that a higher number of comorbidities at the beginning of the follow-up had a negative effect on survival in both ACO and COPD patients.

The overall survival of COPD patients hospitalised for exacerbation was poor as previously described [15] but considering the modern era of rising awareness of COPD and the possibilities of interventions (vaccinations, medication, rehabilitation) and ~~guidelines~~ global statements (GOLD, GINA) still surprisingly poor. In our study, COPD patients with co-existing asthma had significantly better prognosis. In a recent publication the longitudinal change of lung function in ACO patients was favourable compared to COPD patients [16]. On the contrary, in a US based study ACO was associated with higher asthma and COPD severity as well as decreased lung function compared with COPD or asthma alone [17]. It has also been suggested that ACO is a heterogenous group of diseases, with different subtypes for example asthma-predominant ACO and COPD-predominant ACO, with more frequent exacerbations in COPD-predominant ACO-

group [18]. Since we don't have a universally accepted definition of ACO and ACO subtypes, the published data on epidemiology is still controversial.

The significantly better prognosis of ACO patients is ~~a new finding~~in line with previous findings [19, 20]~~( Cosio et al, Suzuki et al)~~ but ~~and~~ the protective factors contributing to better survival are still unclear. Some possible explanatory factors might include patient characteristics such as younger age, female sex or smaller number of pack years, as seen in our study population. The lung function (based on FEV1 and DLCOc) of our ACO patients wasn't better compared to COPD patients, but the variability of airway obstruction and inflammation in asthma might for example result in better response to medication than in ~~non-asthmatic~~ COPD. The use of ICS has been shown to prevent the decline of lung function in asthma patients by preventing severe exacerbation [21~~19~~], and this might reflect on ACO patients, too. The protective factors could also be unrelated to asthma itself, such as the obesity paradox discussed earlier.

It has been shown in earlier studies, that ACO patients are more often younger, female, have higher BMI and a higher burden of comorbidities than compared to patients with asthma or COPD alone [5]. Patients in our ACO group were also younger, more often female and overweight, but we found no difference between ACO and COPD patients when it came to the number of comorbidities. ACO patients also had better survival even when compared to COPD patients with the same amount of or fewer comorbidities at the beginning of the follow up period (Figure 3). Mostly there was no statistically relevant difference between the prevalence of different comorbidities, except for lung cancer, which was more prevalent in COPD patients at the beginning of the follow up. COPD is an independent risk factor for lung cancer development, independent of smoking exposure [22~~20~~]. Patients in the COPD group were older and had more pack years than ACO patients, which could at least play a part in explaining the higher prevalence of lung cancer in this group. However, a reduced risk of lung cancer has also been found in COPD patients with coexisting asthma diagnosis in a large Swedish population-based cohort [23~~1~~]. The~~se findings~~ causes of death were similar to previous findings, where causes of death of COPD patients have been respiratory in 35-57%, cardiovascular in 25-27% and cancer in 20-33% of the cases [12-14].

Very few patients in our material were life-long non-smokers and they all had ACO diagnosis. It is difficult to accept the diagnosis of ACO in a never smoker and to differentiate from chronic asthma but the clinical picture, risk factors such as passive smoking and work-related exposure as well as follow-up data together with response to treatment are helpful.

Survival of ACO patients was also better when taking lung function into account: ACO patients with FEV1 both over and under 50% of their predicted value had superior survival when compared to COPD patients with similar lung function (Figure 2). Better lung function meant longer survival only among ACO patients. Even though FEV1 is one of the several variables used when assessing disease severity and trying to identify patients with an increased risk of

mortality, the degree of airflow limitation alone is not an ideal method when it comes to predicting prognosis of COPD patients [1,~~22~~24]. Comorbidities are common in COPD patients and have been shown to have an impairing influence on prognosis [~~23~~25], as also our study results indicate. A higher number of diagnosed comorbidities at the time of index COPD hospitalisation predicted poorer survival. Therefore, instead of only using lung function tests to evaluate disease severity, a comprehensive assessment of the patient, including the co-existing diseases and their proper treatment, should be made to evaluate disease burden and risks.

When we combined both patient groups, patients with a BMI higher than 25 seemed to have better survival as patients classified as normal or underweight. Even though this difference was not statistically relevant (p = 0.055), this "obesity paradox" has been documented before: obese COPD patients have been shown to have better survival and lower risk of mortality in multiple studies [264]. Overweight has been linked to improved survival in patients hospitalised for exacerbation of COPD both in-hospital and after hospitalisation in earlier studies [2~~75~~,286]. This effect wasn't seen in ACO or COPD as distinct groups. ACO patients had better survival and were more often overweight than COPD patients, and therefore might be over-presented in the higher BMI group and thus improve the survival of patients with higher BMI. However, even though body mass index has long been used to evaluate nutritional risks in patients, other means should also be used when doing a comprehensive assessment of COPD patients nutrition status [297].

A successful 10-year National Asthma Programme was initiated in Finland in 1994. The goal was to reduce the burden of asthma on both individual and national level by enforcing e.g. early diagnosis, active treatment with ICS and self-management, with a focus on educating professionals working in primary care [3028]. The goal was met, and in 1994-2004 the number of hospital days fell by 69% and even though the incidence of asthma still increased, the yearly total costs for asthma were reduced by one-third [230]. This trend has continued in Finland according to a follow-up by Kauppi et al. [2931]. It is possible that these positive results also have a partial effect on COPD patients with asthma in Finland, and thus reflect on the better survival of ACO patients. National COPD Programme 1997-2008 [32] ~~(The 10-year COPD Programme in Finland: effects on quality of diagnosis, smoking, prevalence, hospital admissions and mortality Vuokko L Kinnula, Tuula Vasankari, Eva Kontula, Anssi Sovijarvi, Olli Saynajakangas & Anne Pietinalho Primary Care Respiratory Journal volume 20, pages178-183(2011)~~ was able to end the increase in COPD prevalence, to cut down prevalence of smoking, improved diagnosis and diminished hospitalisation for COPD.

***Limitations***

This was a retrospective hospital register based study~~, so the accuracy of the gathered data can't always be guaranteed~~. Diagnosis for COPD could have been made based on just one spirometry test and the base of diagnosis was not always stated in the patient records, so it is possible the

diagnosis could have been made based on symptoms and an excessive smoking history only in some cases. There were cases where we could not acquire information on lung function, but even though the diagnostic criteria for COPD might not have been met, the overall prognosis remains poor.

***Future implications***

According to our study, the prognosis of both COPD patients hospitalised for exacerbation was worse than the survival in many malignant diseases. An exacerbation of COPD should be treated as a window of opportunity for comprehensive assessment, treatment enhancement and identification and optimal treatment of comorbidities. At the latest at this point should multi-professional teams participate in promoting and supporting smoking cessation, initiating exercise rehabilitation and making a nutritional status assessment for COPD patients. Health coaching and building a treatment partnership with the patient should be incorporated to improve self-management, and the patient should be seen as an active player and key to their own prognosis.

When diagnosing patients with obstructive lung disease, it should be remembered that not all smoker airways obstruction is purely COPD. Identification of a possible underlying asthma-COPD-overlap should be made at an early stage to initiate proper treatment and optimise the patients' prognosis.

## Conclusion

In our study population, the overall survival of COPD patients hospitalised for exacerbation was poor, but the survival of ACO patients was significantly higher than of ~~non-asthmatic~~ COPD patients. Comorbidities are common in both patient groups, and a higher number of comorbidities have a negative effect on survival for both ACO and COPD patients. A comprehensive assessment of patients with obstructive airway disease should be made, not only to optimise the treatment according to the lung disease phenotype but also to identify and manage the possible co-existing diseases.

## Statement of Authorship

The study was planned by T. Harju. L. Peltola, H. Pätsi and T. Harju contributed to the design of the manuscript. L. Peltola and H. Pätsi equally contributed to the acquisition of the data. The data analysis was done by H. Pätsi. All authors contributed to the interpretation of the data and drafting of the manuscript. The final manuscript was written by L. Peltola and H. Pätsi. All authors revised and approved the final manuscript and agree to be fully accountable for ensuring the integrity and accuracy of the work.

## Declaration of Interest

The authors declare, that they have no conflicts of interest.

**Table 1. The differences in patient characteristics between ACO and COPD patient groups**

| | ACO | | | COPD | | | p-value |
|---|---|---|---|---|---|---|---|
| **Variable** | Mean | SD | N | Mean | SD | N | |
| Age (years) | 67.2 | 10.4 | 128 | 70.2 | 10.3 | 86 | <0.05 |
| Sex (male/female) | | | 83/45 | | | 68/18 | |
| Smoking (non/current/ex) | | | 6/61/61 | | | 0/43/43 | |
| Packyears | 39.0 | 16.5 | 106 | 44.4 | 17.0 | 57 | 0.05 |
| BMI | 29.2 | 7.4 | 102 | 25.9 | 7.3 | 61 | <0.01 |
| FEV1 | 1.4 | 0.62 | 94 | 1.6 | 0.74 | 53 | 0.87 |
| __FEV1 (% predicted) | 46.750.5 | 17.517.4 | 9484 | 52.7 | 19.9 | 38 | 0.54 |
| FVC | 2.4 | 0.84 | 93 | 2.6 | 0.94 | 52 | 0.78 |
| __FVC (% predicted) | 63.7 | 16.3 | 93 | 69.3 | 19.8 | 52 | 0.85 |
| FEV1/FVC (%) | 58.6 | 16.1 | 84 | 58.0 | 14.6 | 38 | 0.84 |
| DLCOc (% predicted) | 3.848.9 | 21.92.0 | 83 | 25.33.4 | 20.61.6 | 39 | 0.190.4 |
| __DLCOc (% predicted) | 48.9 | 21.9 | 83 | 25.3 | 20.6 | 39 | 0.4 |
| Number of comorbidities Before the follow-up | 3.1 | 1.71 | 128 | 2.8 | 1.82 | 86 | 0.25 |
| Number of comorbidities After the follow-up | 4.3 | 1.8 | 128 | 3.8 | 1.9 | 86 | 0.5 |

BMI = body mass index; weight (kilograms)/height exp2
FEV1 = forced expiratory volume in one second
FEV1% = FEV1/FVC, forced expiratory volume in one second over forced vital capacity
DLCOc = diffusing capacity of carbon dioxide, corrected for haemoglobin

**Table 2.** The difference in frequencies of comorbidities between ACO and COPD groups at the beginning of follow up.

| Comorbidity | ACO N (%) | COPD N (%) | Total N (%) | p-value |
|---|---|---|---|---|
| Coronary heart disease | 69 (54) | 36 (42) | 105 (49) | 0.8 |
| Hypertension | 64 (50) | 41 (48) | 105 (49) | 0.7 |
| Cardiac arrhythmia | 39 (31) | 18 (21) | 57 (27) | 0.1 |
| Cardiac insufficiency | 47 (37) | 32 (37) | 79 (37) | 0.9 |
| Type 2 diabetes mellitus | 25 (20) | 15 (17) | 40 (19) | 0.7 |
| Chronic bronchitis | 18 (14) | 10 (12) | 28 (13) | 0.6 |
| Osteoporosis | 17 (13) | 8 (9) | 25 (12) | 0.4 |
| Cancer * | 15 (12) | 13 (15) | 28 (13) | 0.5 |
| **Lung cancer** | **4 (3)** | **9 (11)** | **13 (6)** | **0.03** |
| Schizophrenia | 13 (10) | 4 (5) | 17 (8) | 0.1 |
| Connective tissue disease | 11 (9) | 10 (12) | 21 (10) | 0.5 |
| Peripheral atherosclerosis | 14 (11) | 14 (16) | 28 (13) | 0.3 |
| Depression | 18 (14) | 7 (8) | 25 (12) | 0.2 |
| Aneurysm of abdominal aorta | 9 (7) | 6 (7) | 15 (7) | 1.0 |
| Sleep apnoea | 9 (7) | 7 (8) | 16 (8) | 0.8 |
| Gastroesophageal reflux | 16 (13) | 5 (6) | 21 (10) | 0.1 |

* Excluding lung cancer

**Table 3**. The difference in frequencies of underlying cause of deaths between ACO and COPD groups.

| Cause of death | ACO (n=92) | COPD (n=75) | P-value |
|---|---|---|---|
| Respiratory causes | 47 (51%) | 33 (33%) | 0.4 |
| Cardiovascular diseases | 28 (30%) | 22 (29%) | 0.9 |
| Neoplasms~~Cancer~~ | 14 (15%) | 16 (21%) | 0.3 |
| Other | 3 (3%) | 6 (8%) | 0.2 |
| Total | 92 (100%) | 75 (100%) | |

# Legends to figures

**Figure 1:** The survival of ACO patients was significantly better with median survival time of 4,7 years, compared to COPD patients (1.7 years). (p<0.001)

**Figure 2.** Survival time for each group determined by the FEV1 % of predictetd and phenotype (COPD or ACO). Median time of survival was 8.4 years for the patients with ACO and FEV1>50 % predicted, 5.8 years for the patients with ACOS + FEV1 <50 % of predicted, 4.9 for COPD + FEV1 > 50 % of predicted and 3.1 for COPD + FEV1 <50 % of predicted. The impact of Survival in ACO group was significantly worse in cases with FEV1 % <50 % of predicted at the beginning of the follow-up compared to cases with FEV1 >50% predicted had a significant impact oonly between the ACO patients (P < 0.01). FEV1 data was available from 84/128 patients in ACO group and 38/86 in COPD-group.

**Figure 3**: In the group of ACO patients with 0-2 comorbidities median survival was 6.0 years (N= 48), in the group of ACO patients with 3 or more comorbidities the median was 3.7 (N=81), in COPD patients with 0-2 comorbidities the median survival was 2.4 years (N=42) and in COPD patients with 3 or more comorbidities the median survival was 1.1 years (N=43). The impact of the number of comorbidities was significant in both groups (p<0.05 between ACO patients, p < 0.05 between COPD patients).

**Figure 4.** Median survival rate for BMI < 25 group was 3.3 years, For BMI>25 group median survival rate was 5.7, respectively. (p = 0.055)

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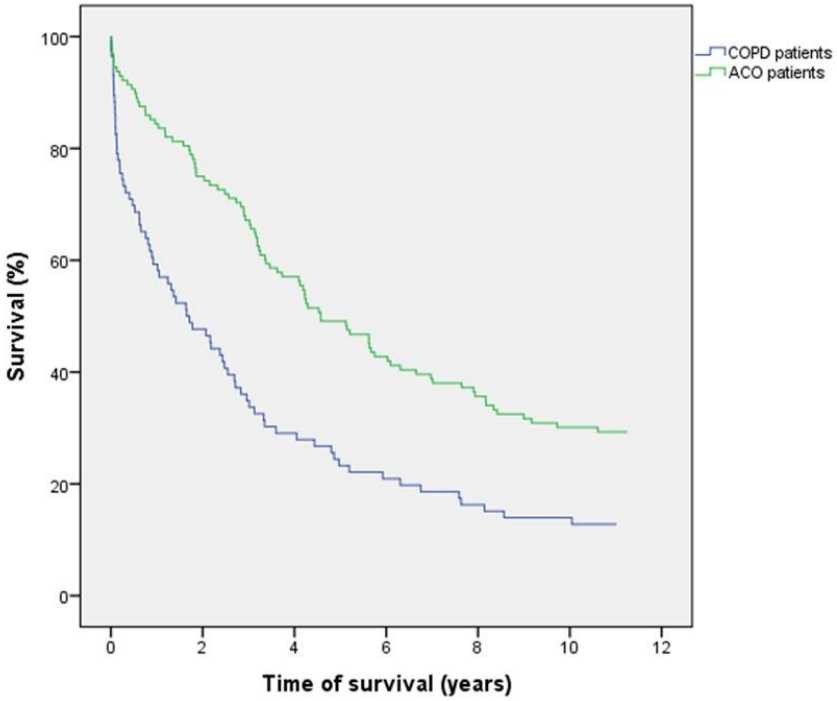


Figure 1. The survival of ACO patients was significantly better with median survival time of 4,7 years, compared to COPD patients (1.7 years). ($p<0.001$)

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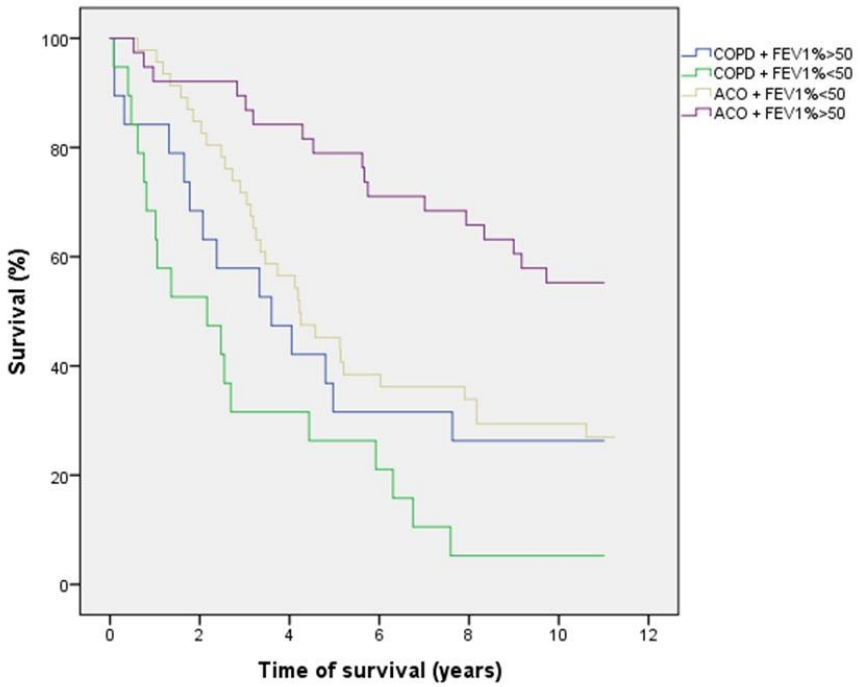


Figure 2. Survival time for each group determined by the FEV1 % of predicetd and phenotype (COPD or ACO). Median time of survival was 8.4 years for the patients with ACO and FEV1>50 % predicted, 5.8 years for the patients with ACOS + FEV1 <50 % of predicted, 4.9 for COPD + FEV1 > 50 % of predicted and 3.1 for COPD + FEV1 <50 % of predicted. The impact of FEV1 % of predicted at the beginning of the follow-up had a significant impact only between the ACO patients ($P < 0.01$).

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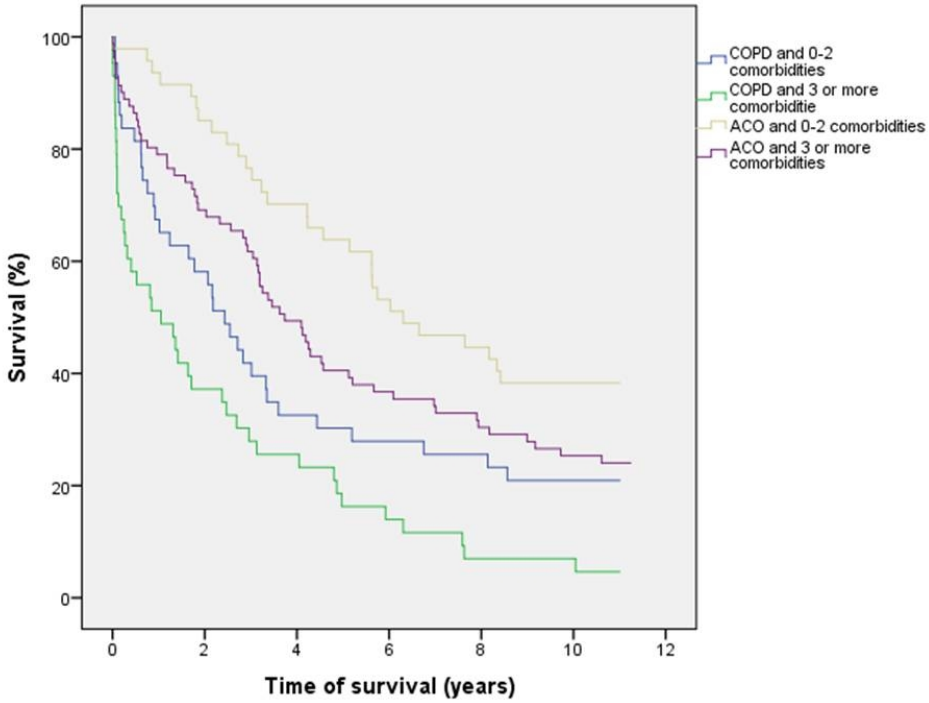


Figure 3. In the group of ACO patients with 0-2 comorbidities median survival was 6.0 years (N= 48), in the group of ACO patients with 3 or more comorbidities the median was 3.7 (N=81), in COPD patients with 0-2 comorbidities the median survival was 2.4 years (N=42) and in COPD patients with 3 or more comorbidities the median survival was 1.1 years (N=43). The impact of the number of comorbidities was significant in both groups ($p<0.05$ between ACO patients, $p < 0.05$ between COPD patients).

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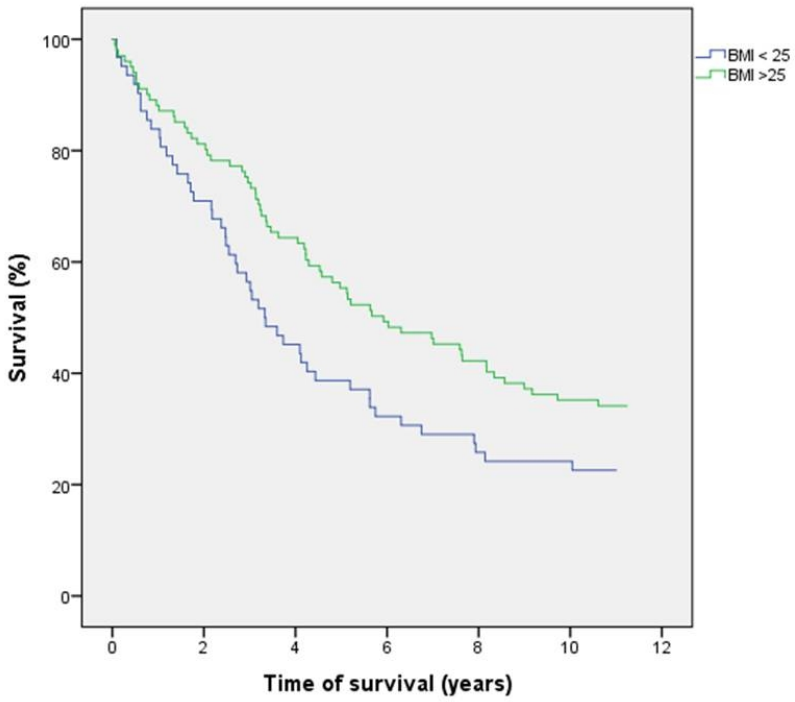


Figure 4. Median survival rate for BMI < 25 group was 3.3 years, For BMI>25 group median survival rate was 5.7, respectively. (p = 0.055)

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