AALBORG UNIVERSITY

STUDENT REPORT

The effect of number and types of comorbidities on all-cause readmission in Danish patients hospitalised with chronic obstructive pulmonary disease

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Abstract

Background: Comorbidities are common in patients with chronic obstructive pulmonary disease (COPD). Previous studies indicate that both an increase in number of comorbidities and specific types of comorbidities may predict readmission risk after a COPD index admission.

Aim: This study analysed the association between number of comorbidities and the risk of 30, 90- and 365-day all-cause readmission in a cohort of Danish patients hospitalised with a COPD exacerbation. Furthermore, this study analysed whether specific types of comorbidities, such as heart diseases, cancer, diabetes, lung diseases, sleep apnea, stroke, ulcers, liver cirrhosis, renal failure and psychological diseases were predictive for 30-, 90 and 365-day all-cause readmission. Lastly, this study examined whether the number or type of comorbidity was a greater predictor for all-cause readmission.

Methods: A retrospective cohort study was conducted based on data collected for all patients hospitalised with a COPD exacerbation in the North Denmark Region in 2018.
Cumulative incidence of readmission was assessed using Kaplan-Meier analysis. Two adjusted Cox proportional hazards models were applied to test the association between 30-, 90- and 365-day readmission and the number and types of comorbidities, respectively. Receiver operating characteristic (ROC) curves were created for both models. The area under the ROC curves (AUC) was calculated to evaluate which of the two models were better at predicting readmission.

Results: A total number of 1439 patients aged ≥40 years were included. All-cause 90- and 365-day readmission was significantly higher in the groups with 2-3 comorbidities (HR: 1.304, 95% confidence interval (CI): 1.051-1.617 and HR: 1.254, CI: 1.057-1.489) and ≥4 comorbidities (HR: 1.984, CI: 1.385-2.842 and HR: 2.129, CI: 1.578-2.872) compared with patients without comorbidities. Comorbidities associated with significantly increased 30-, 90- and 365-day all-cause readmission included atrial fibrillation/flutter and interstitial lung disease (all p-values <0.05). Anxiety was a predictor of 30- and 365-day all-cause readmission (HR: 1.775, CI: 1.136-2.773 and HR: 1.530, CI: 1.144-2.047). Furthermore, asthma and lung cancer were associated with increased 365-day readmission (HR: 1.767, CI: 1.596-1.986 and HR: 1.471, CI: 1.086-1.993). The AUCs for the model with number of comorbidities (AUCs: 0.896, 0.871, 0.875) were higher than those for the model with types of comorbidities (AUCs: 0.800, 0.840, 0.848).

Conclusion: This study found that atrial fibrillation/flutter, interstitial lung disease, asthma, lung cancer, anxiety and having ≥2 comorbidities are risk factors for readmission. Furthermore, the number of comorbidities is a better predictor of 30-, 90- and 365-day readmission than type of comorbidity.

Introduction

Chronic obstructive pulmonary disease (COPD) is a lung disease characterised by chronic airflow limitation, persistent respiratory symptoms, and a progressive and irreversible decline in lung function [1]. It is estimated that the global prevalence of COPD is 10.3% approximately and COPD has become one of the top three causes of death globally [1]. The prevalence and fatality rates are rising [2; 3].

Acute exacerbations of COPD (AECOPD) are common [1] and are defined as an acute worsening in the patient's respiratory symptoms requiring additional therapy [7]. Frequent exacerbations lead to a rapid deterioration of lung function [8], which results in persistent respiratory symptoms, such as dyspnoea, cough and increased sputum production [1; 7]. Furthermore, frequent exacerbations are associated with reduced physical activity and higher hospitalisation and readmission rates [1; 9; 10].

Studies have shown that readmission rates are high among COPD patients following a COPD index admission [11; 12]. Studies suggest that approximately half of all readmissions in COPD patients are due to non-respiratory reasons [17; 18-20] and non-COPD related readmission rates tend to increase over time [22].

According to multiple studies, factors such as high age, being male, previous exacerbations, increased length of initial hospital stay (LOS), alcohol use, smoking and low body mass index (BMI) are known risk factors for increased readmission in COPD patients [12; 15; 23]. Furthermore, comorbidities - defined as the presence of any additional disease co-occurring with a patient's primary disease [112] - have been associated with a significantly increased risk of both COPD-related and non-COPD-related readmissions in COPD patients [12; 24].

A recent systematic review and meta-analysis examined which comorbidities had the highest effect on 30- and 90-day all-cause readmission following a COPD index admission. The study found that the strongest association was with congestive heart failure (CHF), depression and renal failure [53]. Other studies found coronary artery disease and heart failure to be the most important predictors of readmission in COPD patients [12; 17; 21; 25]. According to the newest Global Initiative for Chronic Obstructive Lung Disease (GOLD) report, clinicians should be especially attentive to comorbidities such as ischaemic heart disease, arrhythmias, lung cancer, osteoporosis, gastroesophageal diseases (GERD), diabetes, obstructive sleep apnea, depression and anxiety as these may have a significant impact on disease course in COPD patients [1].

Although specific types of comorbidities are reported to be a risk factor for all-cause readmission in COPD patients, the number of comorbidities is also a risk factor. Multimorbidity - defined as the presence of two or more chronic conditions, where one is not necessarily more central than the others [26] - is associated with increased all-cause

readmission rates 30 and 90 days after a COPD index admission [12; 15; 27]. The more comorbidities a COPD patient has, the higher the risk of getting readmitted [14; 20; 28].

An increase in readmission rates is unfortunate, as studies have found that regardless of readmission cause, COPD patients who are readmitted within 30 and 90 days of index hospitalisation have unfavourable clinical outcomes, i.e. poorer quality of life [4; 13; 14] and increased all-cause mortality for the next three years [9; 15; 16]. Also, readmissions are costly for the healthcare system and result in potentially avoidable resource utilisation [5; 6; 14]. Due to the ageing population [29] and the fact that comorbidities are increasingly frequent at a higher age [30], it is conceivable that there will be a higher number of multimorbid COPD patients in the future [1]. Hence, it is of importance to examine the effect of comorbidities on COPD patients [31].

Hypothesis and aims

Even though previous studies suggest that both specific types of comorbidities and number of comorbidities are important predictors for all-cause readmission in COPD patients [12; 27; 28], none of them compared these predictors. Thus, there is a lack of knowledge in this field. Furthermore, most studies have only analysed the effect of comorbidities on readmission rates at 30 or 90 days of hospital discharge, but the long-term evidence is limited [32].
Thus, in this study it is hypothesised that both number and type of comorbidities have an affect on short- and long-term readmission in COPD patients. Also, it is hypothesised that the number of comorbidities compared to type of comorbidity is greater at predicting 30-, 90- and 365-day readmission in COPD patients.

The primary aim of this study is therefore to determine whether there is a significant effect of number of comorbidities on 30-, 90- and 365-day all-cause readmission in Danish COPD patients.

The secondary aims of this study are to determine whether specific types of comorbidities, including heart diseases, cancer, diabetes, lung diseases, sleep apnea, stroke, ulcers, liver cirrhosis, renal failure and psychological diseases, are predictive for 30-, 90- and 365-day all-cause readmission in Danish COPD patients, and furthermore, to determine whether the number of comorbidities compared to the type of comorbidity is a greater predictor for 30-, 90- and 365-day all-cause readmission in Danish COPD patients.

Methods

Literature search

A systematic literature search was conducted to identify existing published research regarding comorbidities and readmission rates in COPD patients as well as to identify whether the research question previously had been answered.

PubMed, which is a free biomedical database, was searched. Additionally, the biomedical database Embase was searched, as this database can contribute with unique publications not accessible in PubMed [33; 34].

The PICO framework (shown in Table 1) was used in the search strategy to specify and clarify the literature search [35]. In each block different subject headings were searched - MeSH terms in PubMed and Emtree terms in Embase - to obtain a specific search with high precision [36]. By using subject headings, all the literature covering the field will typically not be found [37], thus, free-text terms were also searched. The free-text terms were for example found by using synonym dictionaries. The free-text terms and subject headings were within each block combined with the Boolean operator "OR". Each block was then combined with the Boolean operator "AND".

Table 1.

PICO framework: The combinations of free-text terms, MeSH terms and Emtree terms used to build block searches in PubMed and Embase.

PubMed 8.10.22, 4:31 pm	**Keywords**	**Search strategies**
Block P (population)	***COPD*** patients admitted due to COPD exacerbation	"pulmonary disease, chronic obstructive"[MeSH Terms] OR "acute exacerbation of COPD"[Text Word] OR "acute exacerbation of chronic obstructive pulmonary disease"[Text Word] OR "AECOPD"[Text Word] OR "respiratory system disease*"[Text Word] OR "COPD"[Text Word] OR "copd patient*"[Text Word] OR "copd exacerbation*"[Text Word] OR "chronic obstructive pulmonary disease*"[Text Word] OR "chronic obstructive lung disease*"[Text Word] OR "COAD"[Text Word] OR "chronic obstructive airway disease*"[Text Word] OR "chronic airflow obstruction*"[Text Word] OR "pulmonary emphysema"[Text Word] OR "lung emphysema"[Text Word] OR "chronic bronchitis"[Text Word]
Block I (intervention)	Having one or more ***comorbidities***	"Comorbidity"[MeSH Terms] OR "comorbidit*"[Text Word] OR "multimorbidit*"[Text Word] OR "co morbid condition*"[Text Word] OR "concomitant disease*"[Text Word] OR "concomitant

		disorder*"[Text Word] OR "concurrent disease*"[Text Word] OR "concurrent disorder*"[Text Word] OR "co diagnos*"[Text Word] OR "secondary diagnos*"[Text Word]) OR "concurrent chronic disorder*"[Text Word] OR "multiple condition*"[Text Word] OR "multiple illness*"[Text Word] OR "multiple disease*"[Text Word] OR "multiple disorder*"[Text Word] OR "multiple chronic condition*"[Text Word] OR "multiple chronic illness*"[Text Word] OR "multiple chronic disease*"[Text Word] OR "multiple chronic disorder*"[Text Word] OR "concurrent chronic condition*"[Text Word] OR "concurrent illness*"[Text Word] OR "concurrent chronic medical condition*"[Text Word] OR "concurrent medical condition*"[Text Word] OR "multiple chronic health condition*"[Text Word] OR "co existing disease*"
Block C (comparison)	Not having comorbidities	*Not applicable*
Block O (outcome)	***All-cause readmission*** after a COPD index admission	"Patient Readmission"[MeSH Terms] OR "readmission rate*"[Text Word] OR "all cause readmission*"[Text Word] OR "unexpected hospital readmission*"[Text Word] OR "unplanned hospital readmission*"[Text Word] OR "unexpected readmission*"[Text Word] OR "unplanned readmission*"[Text Word] OR "readmission*"[Text Word] OR "patient readmission*"[Text Word] OR "hospital readmission*"[Text Word] OR "readmission risk*"[Text Word] OR "readmit*"[All Fields] OR "re entr*"[All Fields] OR 'rehospitali*'
Embase 8.10.22, 5:28 pm	**Keywords**	**Search strategies**
Block P (population)	***COPD*** patients admitted due to COPD exacerbation	'chronic obstructive lung disease'/exp OR 'acute exacerbation of copd' OR 'acute exacerbation of chronic obstructive pulmonary disease' OR 'aecopd' OR 'respiratory system disease*' OR 'copd' OR 'copd patient*' OR 'copd exacerbation*' OR 'chronic obstructive lung disease*' OR 'coad' OR 'chronic obstructive airway disease*' OR 'chronic airflow obstruction*' OR 'pulmonary emphysema' OR 'lung emphysema' OR 'chronic bronchitis' OR 'chronic obstructive lung disease*'
Block I (intervention)	Having one or more ***comorbidities***	'multiple chronic conditions'/exp OR 'comorbidity'/exp OR 'comorbidit*' OR 'multimorbidit*' OR 'co morbid condition*' OR 'concomitant disease*' OR 'concomitant disorder*' OR 'concurrent disease*' OR 'concurrent disorder*' OR 'concurrent chronic disorder' OR 'concomitant chronic disorder*' OR 'co diagnos*' OR 'secondary diagnos*' OR 'multiple chronic condition*' OR 'multiple chronic disease*' OR 'multiple chronic disorder*' OR 'multiple condition*' OR 'multiple illness*' OR 'multiple disease*' OR

		'multiple disorder*' OR 'multiple chronic illness*' OR 'simultaneous chronic medical condition*' OR 'concurrent chronic condition*' OR 'simultaneous chronic illness*' OR 'concurrent illness*' OR 'concurrent chronic medical condition*' OR 'concurrent medical condition*' OR 'multiple chronic health condition*' OR 'co existing disease*'
Block C (comparison)	Not having comorbidities	*Not applicable*
Block O (outcome)	***All-cause readmission*** after a COPD index admission	'hospital readmission'/exp OR 'hospital readmission*' OR 'readmission rate*' OR 'readmission*' OR 'unexpected hospital readmission*' OR 'unplanned hospital readmission*' OR 'unexpected readmission*' OR 'unplanned readmission*' OR 'all cause readmission*' OR 'patient readmission*' OR 'readmission risk*' OR 're entr*' OR 'rehospitali*'

Two reviewers independently screened relevant titles and abstracts to determine whether they met the inclusion criteria. Studies were included that investigated: a) readmission after an initial admission with COPD exacerbation, b) all-cause readmission to a hospital, not only to an emergency department etc., and c) analysed the effect of specific comorbidities or number of comorbidities on readmission rates in COPD patients. Quality of the included studies was assessed by using relevant checklists for the different study types in the articles [38].

In figure 1 the results of the literature search are shown. A total of 65 studies were included.

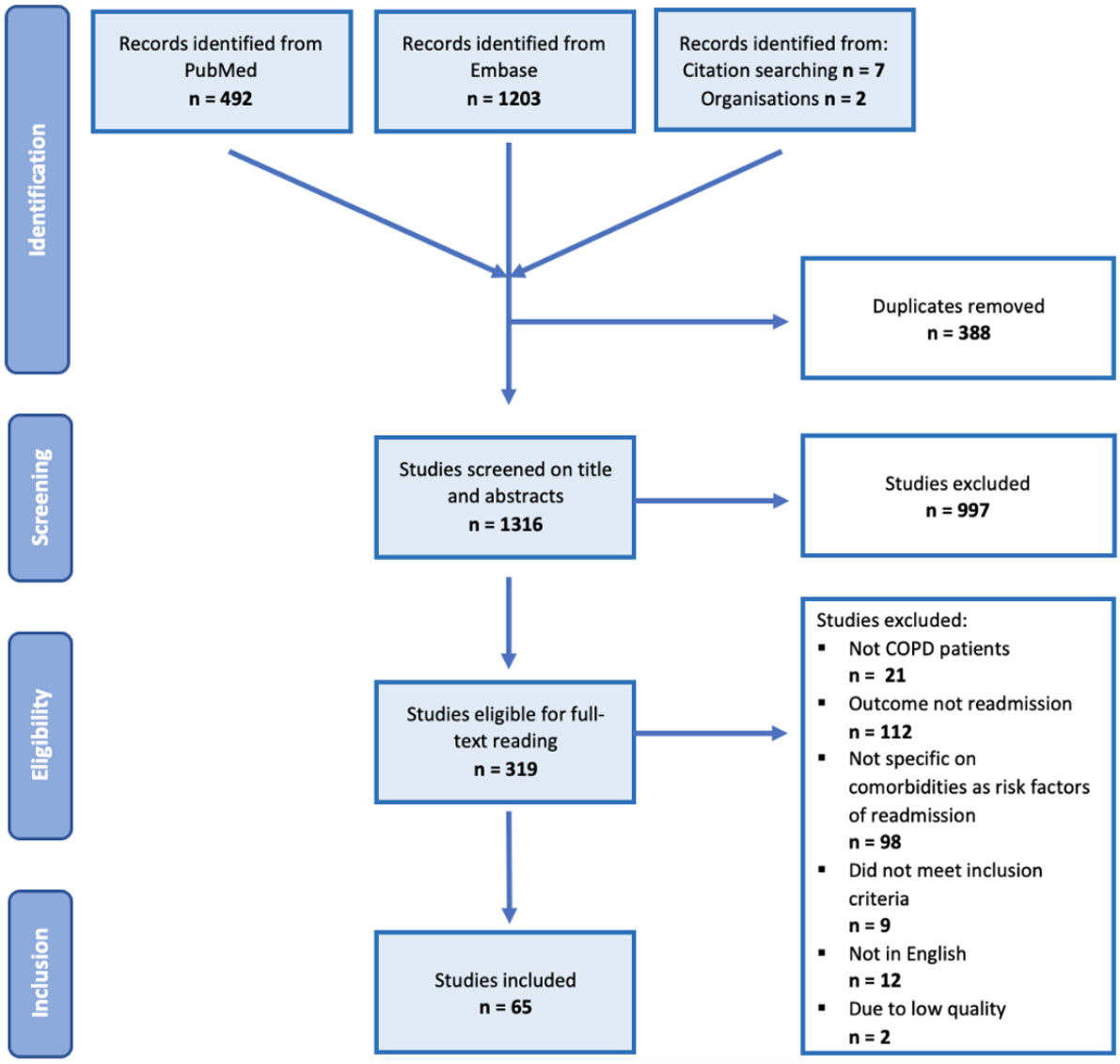

Figure 1. *PRISMA flow diagram of the search, screening and inclusion process.*

Study design

This retrospective cohort study was conducted in The North Denmark Region, which covers a population of ~ 0.60 million people (about 10% of the Danish population) [39]. Denmark is a unique setting for conducting registry-based studies, as it has a long tradition of continuous registration of high-quality medical data [40-42]. The Danish National Patient Registry (DNPR) provides information on all inpatient admissions to hospital since 1977 as well as all outpatient clinic and emergency room visits since 1995 [41]. Since 1994 each admission has been registered in the DNPR with one primary diagnosis and up to several secondary diagnoses according to the 10th revision of the International Classification of Diseases (ICD-10). Furthermore, state health care is free of charge to anyone living and working in Denmark,

guaranteeing universal medical care for all Danish residents and partial reimbursement for prescribed medications [40].

In this study, data was collected for the Exacerbations of COPD; identification of risk factors for readmission (EXAcise) database from electronic medical records of patients admitted to any of the hospitals in The North Denmark region in 2018 with the diagnosis exacerbation of chronic obstructive pulmonary disease (COPD). The database was created, and date registered using REDCap® (Vanderbilt University, Nashville, Tennessee, USA). Data was collected according to a protocol by Hansen et. al from 2021 [43]. The database was validated by another entry clerk uninvolved in this study. The entry clerk randomly re-registered data on 10% of the study population. Data were compared by means and a max difference of 5% was allowed. Data were revisited if a difference more than 5% was observed.

Study population

The study population consisted of all COPD patients in The North Denmark region who had been admitted to any of the hospitals in the region between January 1st and December 31st in 2018. An admission was defined as an overnight stay in hospital. Index admission was chosen to be the first admission within 2018. Index admission diagnoses were defined according to Thomsen et al. [44]. Thus, patients with an ICD-10 hospital discharge diagnosis code of COPD (J44) were included. COPD diagnoses were included if they were coded either as a primary or a secondary diagnosis combined with a primary diagnosis code for pneumonia (J13-J18) or acute respiratory failure (J96) during the same index admission [44].

Patients were excluded if they a) were aged under 40 years due to the potential risk of misclassification of asthma as COPD [45; 46], b) were hospitalised with indications other than AECOPD, c) died in-hospital during index admission, or d) were not resident in the North Denmark region to make sure that potential future readmissions were accessible. Furthermore, patients that developed pneumonia or AECOPD during index admission due to other diagnoses were excluded as instructed by Hansen et al. 2021 [43]. Outpatient surgeries or emergency room visits were neither included as index admissions or readmissions.

To ensure that patients were not wrongly excluded, their individual medical records were checked manually in terms of examining whether a COPD patient had been treated for AECOPD or pneumonia without the right ICD-code being registered.

Outcome

The primary outcome of interest was readmission, defined as a hospitalisation at any hospital in the region for any reason occurring within 30, 90 and 365 days of discharge from a COPD index admission. Time to readmission was defined as the number of days from discharge (day 0) to the first admission up to day 30, 90 and 365.
The secondary outcome measure was mortality. Date of death was registered for the patients who died within 30, 90 and 365 days after index admission.

Collection of covariates

The major independent variable was a set of 17 comorbidities in accordance with the COPD specific comorbidity test (COTE) [43]. Relevant comorbidities registered were chronic heart failure, coronary artery disease, atrial fibrillation/flutter, stroke, lymphoma/leukemia, lung cancer, all other cancers, interstitial lung disease, asthma, chronic renal failure, gastric- or duodenal ulcers, liver cirrhosis, diabetes mellitus type 1 and 2, depression and anxiety. Furthermore, sleep apnea was registered as a comorbidity [1].

Data on comorbidities was collected from the patient's admission record. If the patient's medical list indicated that the patient had a relevant comorbidity not mentioned in the admission record, with no doubt to the indication for the medication, the comorbidity was included. Comorbidities were categorised into having 0, 1, 2-3 and ≥ 4 comorbidities.

Besides comorbidities, age, gender and smoking status were included. Age was categorised into six groups: 40-49, 50-59, 60-69, 70-79, 80-89 and ≥ 90 years with 70-79 years being the reference group. Gender and smoking were dichotomised, where smokers were divided into two groups; former/never smokers and active smokers. Other covariates were registered as described in the protocol by Hansen et al. [43].

Statistical analysis

Descriptive statistics were used to summarise the data. Categorical variables were expressed as frequencies and percentages, while continuous variables were summarised as mean ± standard deviation (SD) if normally distributed or median and interquartile range (IQR) otherwise.
First, baseline demographics and characteristics were compared between the groups: *a)* comorbidities categorised in number vs no comorbidities and *b)* types of comorbidities vs no comorbidities. Second, baseline characteristics were compared between readmitted and not readmitted patients within 30, 90 and 365 days, respectively. Categorical variables were

compared using the chi-square or Fisher's exact test. Continuous variables were compared using unpaired t-test if normally distributed or Mann-Whitney U tests if not normally distributed.

Kaplan-Meier curves were used to compare the cumulative incidence of readmission (time to readmission) of patients without comorbidities and with 1, 2-3 and ≥ 4 comorbidities, respectively. Furthermore, patients with and without the 17 types of comorbidities were compared. The log-rank test was conducted to check for statistical significance.

Cox proportional hazards regression models were applied to assess predictors of 30-, 90- and 365-day all-cause readmission, also taking other covariates into account. To test the proportional hazards assumptions the interaction between the time measure and the covariates in the models were tested [47]. Results were presented as hazard ratios (HR).
Two Cox regression models were applied, one with number of comorbidities (model A) and one with types of comorbidities (model B) as main independent variables. In model A comorbidities were treated as nominal variables with 0 comorbidities being the reference group. In model B all 17 comorbidities were treated as dichotomous variables. In both models it was adjusted for gender, age and smoking status.
The two Cox regression models were repeated for mortality.

To compare which of the two models were better at predicting readmission, receiver operating characteristic curves (ROC curves) were created for both models. Hypothesis tests were done to evaluate whether the area under the ROC curves (AUC) differed significantly from 0.5 [48]. For ROC curves for both models at 30, 90 and 365 days, respectively, AUC was calculated and compared to determine which model was better at predicting readmission. The closer the AUC values were to 1.0 the better the model was at predicting readmission. AUC results were considered good for AUC values above 0.8 [49; 50].

In all analyses a confidence interval (CI) of 95% was reported and a *p*-value of <0.05 was considered statistically significant.
All data were analysed using the Software Statistical Package for the Social Sciences (SPSS), version 28.0.1.1.

Ethics

The study was registered in the North Denmark Region with ID-number F2022-123. The study was approved by the Danish Patient Safety Authority with case number 31-1521-34. No ethical approval was required for this study.

Results

Study population and characteristics

As shown in Figure 2, a total of 1776 patients were identified from the database of the North Denmark Region. Data collection was initiated in September 2020, and in September 2022 data had been collected on all patients. In total 1532 patients were registered in the EXAcise database. Out of these, a final number of 1439 patients were included in this study.

Through the validation proces no systematic errors were identified in the primary data registry.

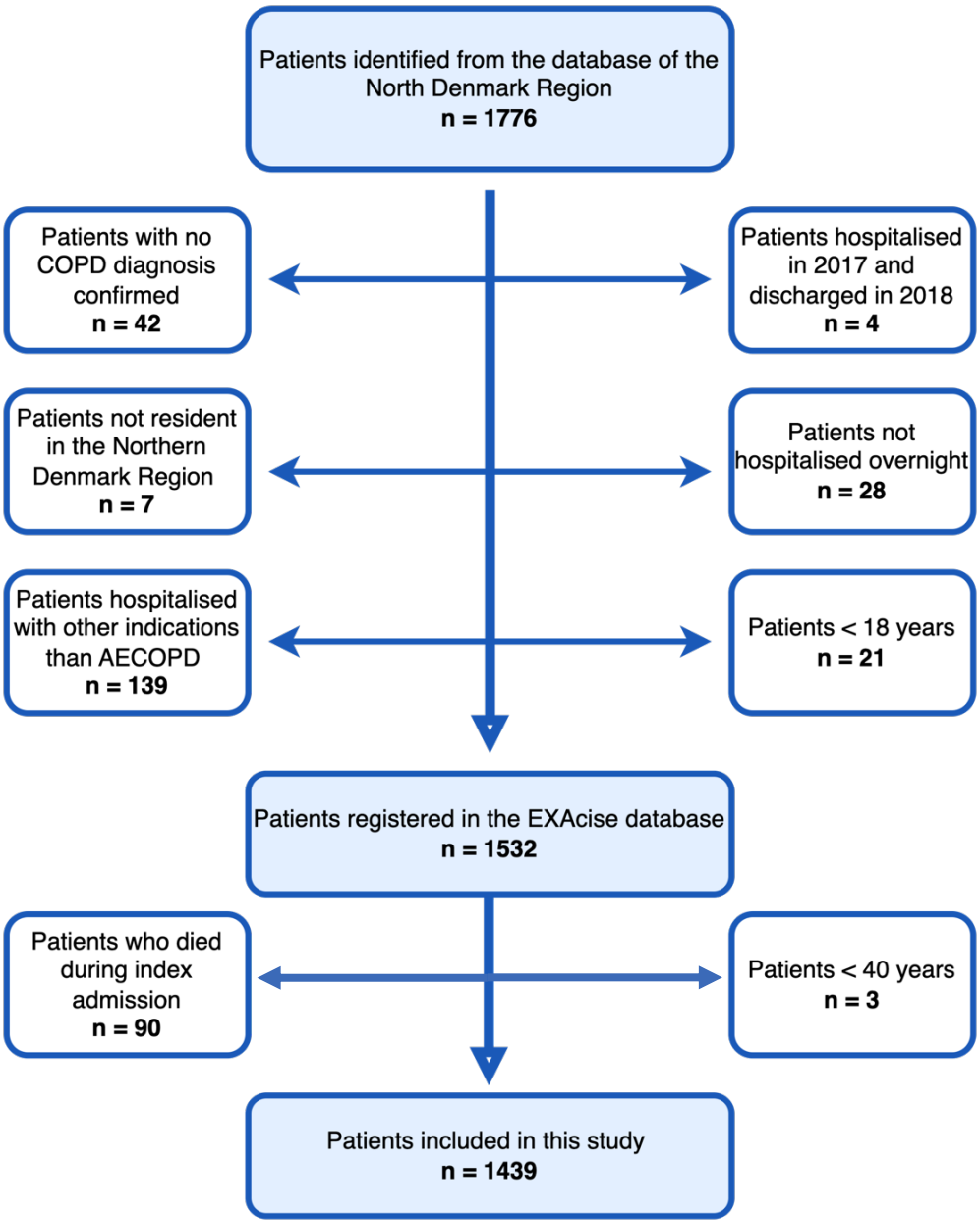

Figure 2. *Cohort selection process and the exclusion criteria.*

Note. Abbreviations: COPD = chronic obstructive pulmonary disease. AECOPD = acute exacerbations of COPD. EXAcise = Exacerbations of COPD; identification of risk factors for readmission.

Table 2 shows that baseline characteristics were equally distributed between the readmitted and non-readmitted groups in terms of age and gender. On index admission the COPD patients with 90- and 365-day readmissions had on average more comorbidities compared to the non-readmitted group ($p < 0.001$).

Table 2.
Baseline characteristics of the cohort classified into patients with and without 30-, 90- and 365-day readmissions.

	No readmission *n = 1078 (74.9%)*	**30-day readmission** *n = 361 (25.1%)*	**No readmission** *n = 867 (60.3%)*	**90-day readmission** *n = 572 (39.7%)*	**No readmission** *n = 547 (38.0%)*	**365-day readmission** *n = 892 (62.0%)*
Male *n (%)*	473 (74.4)	163 (25.6)	375 (59.0)	261 (41.0)	238 (37.4)	398 (62.6)
Female *n (%)*	605 (25.6)	198 (74.4)	492 (41.0)	311 (59.0)	127 (62.6)	494 (37.4)
Age in years						
mean (SD)	74.5 (10.2)	74.5 (10.3)	74.3 (10.2)	74.7 (10.4)	74.1 (10.5)	74.7 (10.1)
median (IQR)	75.0 (15.0)	75.0 (13.0)	75.0 (15.0)	76.0 (13.0)	74.0 (15.0)	75.0 (13.8)
Smoking status						
Active smoker n (%)	406 (37.7)	137 (38.0)	341 (39.3)	202 (35.3)	213 (38.9)	330 (37.0)
Non-smoker n (%)	565 (52.4)	188 (52.1)	443 (51.1)	310 (54.2)	280 (51.2)	473 (49.0)
Missing values	107 (9.9)	36 (10.0)	83 (9.6)	60 (10.5)	54 (9.9)	89 (10.0)
Number of comorbidities						
mean (SD)	1.23 (1.2)	1.35 (1.2)	1.17 (1.1)	1.40 (1.2)*	1.10 (1.0)	1.36 (1.2)*
median (IQR)	1.00 (2.0)	1.00 (2.0)	1.00 (2.0)	1.00 (2.0)	1.00 (2.0)	1.00 (2.0)

Note.
* $p < 0.001$.
**$p < 0.005$.
Abbreviations: SD = standard deviation. IQR = interquartile range.

Distribution of comorbidities

Figure 3A and 3B illustrate the distribution of types of comorbidities and number of comorbidities. As shown in Table 3, there was a significant difference in number of comorbidities between gender, smoking status and age. Patients with ≥ 2 comorbidities were more likely men and had a higher age compared with patients without comorbidities.

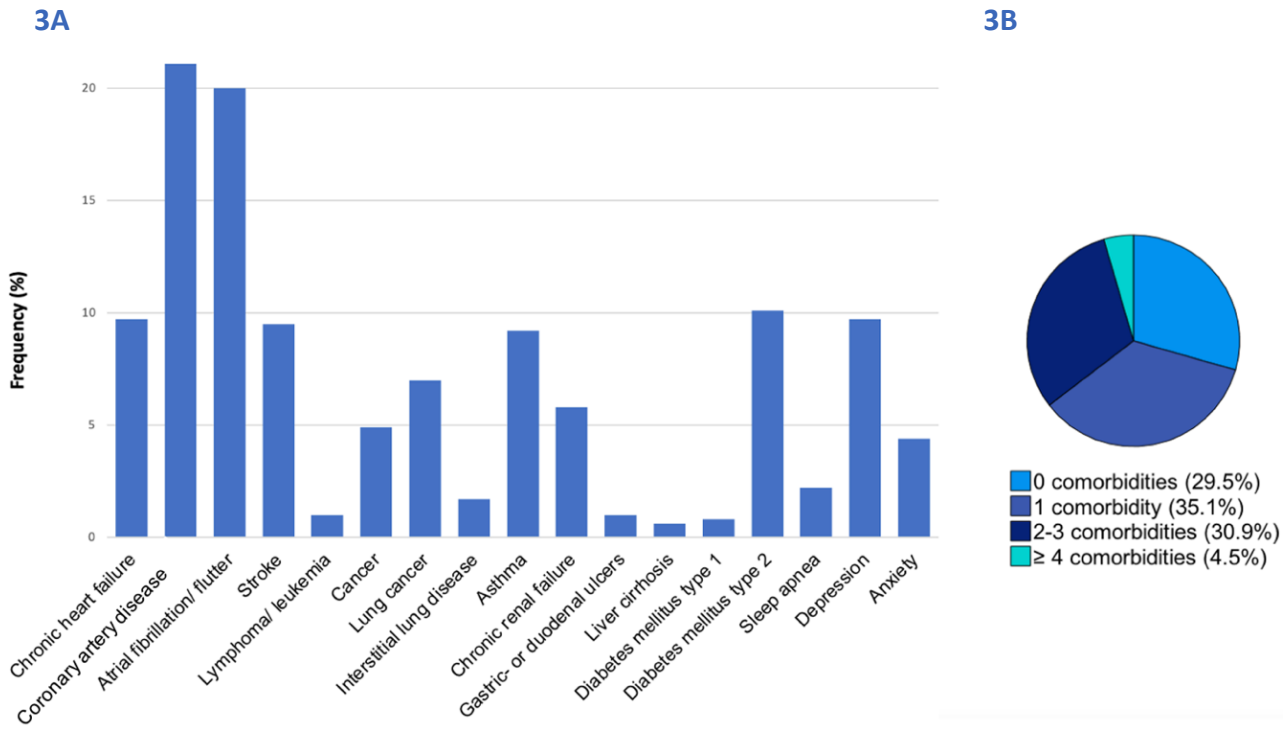

Figure 3: A. *Distribution types of comorbidities in all 1439 patients with a COPD index admission in 2018 in the North Denmark Region,* and **B.** *Distribution of number of comorbidities in all 1439 patients with a COPD index admission in 2018 in the North Denmark Region.*

Table 3.

Baseline characteristics of the cohort classified into number and types of comorbidities.

	Male *n* = 636 (44.2%)	**Female** *n* = 803 (55.8%)	**Age** *mean (SD)*	*median (IQR)*	**Smoker** *n* = 543 (37.7%)	**Non-smoker** *n* = 753 (52.3%)
Number [a]						
0	168 (26.4)	256 (31.9)	72.9 (10.7)	74.0 (15.0)	166 (30.1)	220 (29.2)
1	217 (34.1)	288 (35.9)	75.2 (10.0)	74.0 (14.5)	202 (37.2)	255 (33.9)
2-3	218 (34.3)	226 (28.1)**	76.3 (9.6)	77.0 (12.0)*	159 (29.2)	239 (31.7)**
≥ 4	33 (5.2)	32 (4.1)	76.7 (8.8)	77.0 (12.0)**	16 (2.9)	39 (5.2)
Type [b]						
Chronic heart failure	79 (12.4)	60 (7.5)**	*Yes:* 76.2 (9.6) *No:* 74.3 (10.3)	78.0 (14.0) 75.0 (14.0)**	*Yes:* 47 (8.7) *No:* 496 (91.3)	73 (9.7) 680 (90.3)
Coronary heart disease	159 (25.0)	145 (18.1)*	*Yes:* 77.0 (9.3) *No:* 73.8 (10.4)	78.0 (13.0) 74.0 (15.0)*	*Yes:* 110 (20.3) *No:* 433 (79.8)	156 (20.8) 597 (79.3)
AF/ AFL	151 (23.7)	137 (17.1)**	*Yes:* 79.0 (8.2) *No:* 73.4 (10.4)	79.0 (12.0) 74.0 (15.0)*	*Yes:* 91 (16.8) *No:* 452 (83.2)**	161 (21.4) 592 (78.6)

Stroke	65 (10.2)	71 (8.8)	*Yes:* 75.3 (9.4)	75.0 (14.0)	*Yes:* 45 (8.3)	73 (9.7)
			No: 74.4 (10.3)	75.0 (14.0)	*No:* 498 (91.7)	680 (90.3)
Lymphoma / Leukemia	6 (0.9)	9 (1.1)	*Yes:* 74.4 (12.4)	70.0 (22.0)	*Yes:* 4 (0.7)	9 (1.2)
			No: 74.5 (10.2)	75.0 (14.0)	*No:* 539 (99.3)	744 (98.9)
Cancer	61 (9.6)	40 (5.0)*	*Yes:* 77.2 (9.2)	78.0 (13.0)	*Yes:* 30 (5.5)	64 (8.5)
			No: 74.3 (10.3)	75.0 (14.0)**	*No:* 513 (94.5)	689 (91.5)
Lung cancer	31 (4.9)	39 (4.9)	*Yes:* 74.7 (7.3)	75.0 (10.0)	*Yes:* 30 (5.5)	34 (4.5)
			No: 74.5 (10.4)	75.0 (14.0)	*No:* 513 (94.5)	719 (95.5)
Interstitial lung disease	16 (2.5)	8 (1.0)**	*Yes:* 77.1 (10.1)	76.0 (16.0)	*Yes:* 4 (0.7)	16 (2.1)
			No: 74.4 (10.2)	75.0 (14.0)	*No:* 539 (91.7)	737 (97.9)
Asthma	43 (6.8)	89 (11.1)**	*Yes:* 72.2 (11.2)	72.5 (16.0)	*Yes:* 48 (8.8)	78 (10.4)
			No: 74.7 (10.1)	75.0 (14.0)**	*No:* 495 (91.2)	675 (89.6)
Chronic renal failure	52 (8.2)	31 (3.9)*	*Yes:* 80.4 (8.0)	81.0 (12.0)	*Yes:* 20 (3.7)	53 (7.0)
			No: 74.1 (10.3)	75.0 (15.0)*	*No:* 523 (96.3)**	700 (93.0)
Ulcers	6 (0.9)	9 (1.1)	*Yes:* 77.4 (8.0)	80.0 (12.0)	*Yes:* 6 (1.1)	9 (1.2)
			No: 74.5 (10.3)	75.0 (14.0)	*No:* 537 (98.9)	744 (98.8)
Liver cirrhosis	2 (0.3)	7 (0.9)	*Yes:* 71.0 (6.5)	70.0 (7.0)	*Yes:* 3 (0.6)	5 (0.7)
			No: 74.5 (10.3)	75.0 (14.0)	*No:* 540 (99.4)	748 (99.3)
Diabetes mellitus type 1	5 (0.8)	7 (0.9)	*Yes:* 73.6 (6.1)	74.0 (6.0)	*Yes:* 5 (0.7)	5 (0.7)
			No: 74.5 (10.3)	75.0 (14.0)	*No:* 538 (71.4)	748 (99.3)
Diabetes mellitus type 2	128 (20.1)	128 (16.0)	*Yes:* 75.0 (9.5)	75.0 (13.0)	*Yes:* 91 (12.1)	133 (17.7)
			No: 74.4 (10.4)	75.0 (15.0)	*No:* 452 (60.0)	620 (82.3)
Sleep apnea	22 (3.5)	9 (1.1)**	*Yes:* 70.3 (9.2)	71.0 (13.0)	*Yes:* 7 (0.9)	17 (2.6)
			No: 74.6 (10.3)	75.0 (14.0)**	*No:* 536 (98.7)	736 (97.7)
Depression	36 (5.7)	103 (12.8)*	*Yes:* 73.4 (10.5)	74.0 (16.0)	*Yes:* 61 (11.2)	67 (8.9)
			No: 74.6 (10.2)	75.0 (14.0)	*No:* 482 (88.8)	686 (91.1)
Anxiety	17 (2.7)	47 (5.9)**	*Yes:* 70.5 (10.5)	73.0 (12.0)	*Yes:* 29 (5.3)	32 (4.2)
			No: 74.7 (10.2)	75.0 (14.0)**	*No:* 514 (94.7)	721 (95.8)

Note.
* $p < 0.001$.
** $p < 0.05$.

[a] All the groups with number of comorbidities are compared with the zero comorbidity group (reference group).

[b] Yes = mean age ± SD and median ± IQR in patients having the comorbidity. No = mean age ± SD and median ± IQR in patients not having the comorbidity.

Abbreviations: SD = standard deviation. IQR = interquartile range. AF = atrial fibrillation. AFL = atrial flutter. Ulcers = gastric or duodenal ulcers.

Number of comorbidities and readmission

Figure 4A shows the log-rank test comparing the Kaplan-Meier curves (i.e. time to readmission) between patients without comorbidities and with 1, 2-3 and ≥ 4 comorbidities, respectively. The Kaplan-Meier plot showed that patients with 2-3 and ≥ 4 comorbidities had significantly shorter readmission free survival time compared with patients without comorbidities at 90- and 365-day follow-up (all *p*-values <0.05).

Results from the adjusted Cox proportional hazards regression models (Table 4A) reported a significantly higher all-cause readmission at 90- and 365-day follow-up among patients with 2-3 comorbidities (HR: 1.305, 95% CI: 1.051-1.618, and HR: 1.254, 95% CI: 1.059-1.489) and ≥ 4 comorbidities (HR: 1.984, 95% CI: 1.386-2.839 and HR: 2.129, 95% CI: 1.578-2.870) compared with patients without comorbidities.

Figure 4A

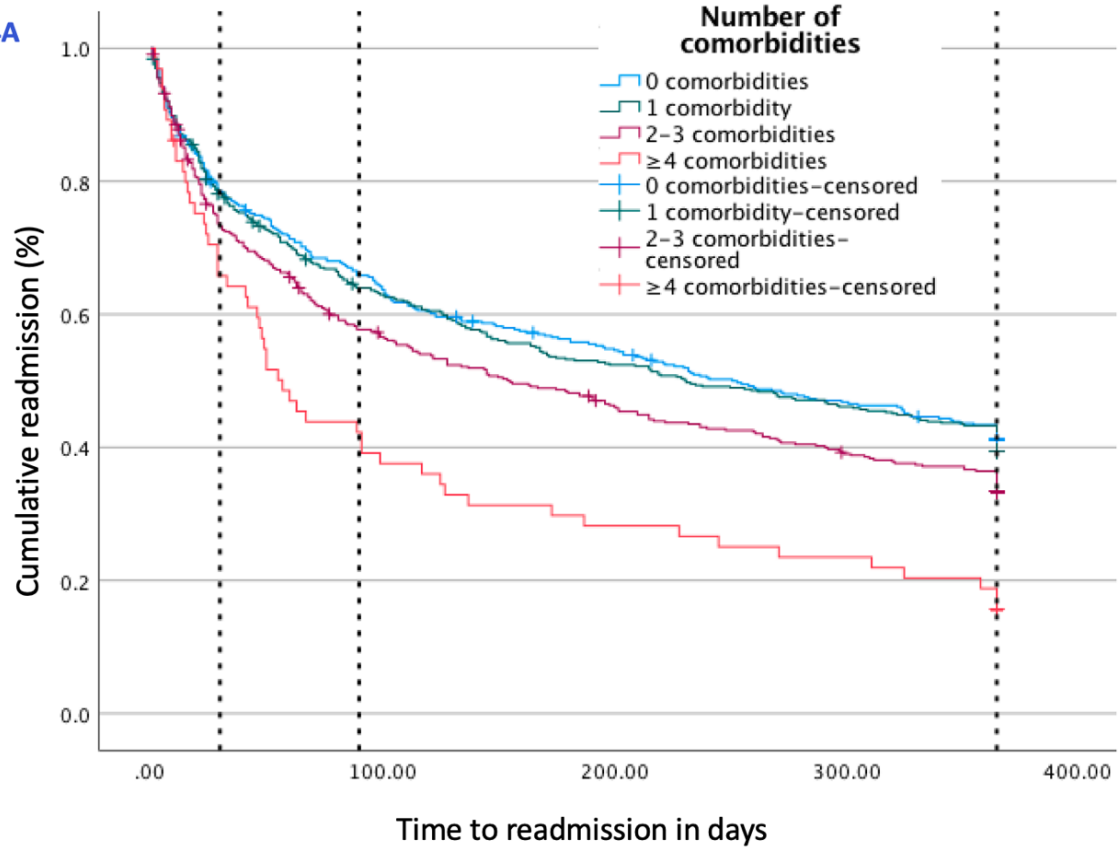

Figure 4B

	Cumulative readmission (%) at:		
	30 days	**90 days**	**365 days**
Number of comorbidities			
0 (reference group)	23%	36%	59%
1	24%	38%	58%
2-3	29%	43% *	66% *
≥ 4	36%	58% **	82% **
Type of comorbidity			
Chronic heart failure	10%	41%	71% **
Coronary artery disease	6%	39%	65%
Atrial fibrillation/ flutter	30% *	53%	72% *
Stroke	7%	39%	61%
Lymphoma/ leukemia	20%	32%	52%
Cancer	17%	41%	65%
Lung cancer	18%	41%	68%
Interstitial lung disease	6%	59%	75% **
Asthma	7%	36%	61% **
Chronic renal failure	20%	40%	67%
Gastric/duodenal ulcers	0%	40%	73%
Liver cirrhosis	0%	45%	55%
Diabetes mellitus type 1	0%	33%	68%
Diabetes mellitus type 2	10%	43%	65%
Sleep apnea	3%	42%	72%
Depression	6%	40%	71%
Anxiety	35% **	44% **	80% **

Figure 4: A. *Kaplan-Meier curves showing the cumulative time to readmission over the study period of 365 days for the 'number of comorbidities' subgroup*, and **B.** *Cumulative readmission at 30, 90 and 365 days for the subgroups of types and number of comorbidities.*

Note.
Horizontal lines indicate 30, 90 and 365 days.
Subgroups of number of comorbidities were compared with the 0 comorbidity group (reference group). Patients with the specific types of comorbidities were compared with patients who did not have these comorbidities (reference group).
* $p < 0.001$, according to the log rank test.
** $p < 0.05$, according to the log rank test.

Table 4.

A. *Adjusted hazard ratios with 95% confidence intervals testing associations between probability of all-cause 30-, 90- and 365-day readmission and number of comorbidities.*

B. *Adjusted hazard ratios with 95% confidence intervals testing associations between probability of all-cause 30-, 90- and 365-day readmission and types of comorbidities.*

4A *Model A*	30 days			90 days			365 days		
	HR	**CI (95%)**	***p***	**HR**	**CI (95%)**	***p***	**HR**	**CI (95%)**	***p***
Number [a]									
0	1.0			1.0			1.0		
1	0.974	0.739 – 1.286	*NS*	1.070	0.862 – 1.329	*NS*	1.046	0.882 – 1.240	*NS*
2-3	1.115	0.842 – 1.475	*NS*	1.305	1.051 – 1.618	**	1.254	1.059 – 1.489	**
≥ 4	1.106	0.649 – 1.895	*NS*	1.984	1.386 – 2.839	*	2.129	1.578 – 2.870	*

4B *Model B*	30 days			90 days			365 days		
	HR	**CI (95%)**	***p***	**HR**	**CI (95%)**	***p***	**HR**	**CI (95%)**	***p***
Type [b]									
Heart failure	0.827	0.554 – 1.230	*NS*	0.988	0.751 – 1.302	*NS*	1.090	0.874 – 1.360	*NS*
CAD	0.838	0.630 – 1.113	*NS*	0.947	0.771 – 1.163	*NS*	1.069	0.907 – 1.259	*NS*
AF / AFL	1.596	1.231 – 2.074	*	1.630	1.339 – 1.982	*	1.461	1.240 – 1.721	*
Stroke	1.026	0.711 – 1.478	*NS*	1.051	0.798 – 1.389	*NS*	0.994	0.789 – 1.248	*NS*
Lymphoma / Leukemia	1.618	0.661 – 3.965	*NS*	1.124	0.497 – 2.540	*NS*	0.964	0.476 – 1.954	*NS*
Cancer	1.265	0.842 – 1.909	*NS*	1.151	0.836 – 1.579	*NS*	1.180	0.913 – 1.519	*NS*
Lung cancer	1.178	0.722 – 1.939	*NS*	1.417	0.981 – 2.053	*NS*	1.469	1.094 – 1.999	**
Interstitial lung disease	2.047	1.037 – 4.038	**	1.774	1.029 – 3.050	**	1.711	1.062 – 2.759	**
Asthma	0.845	0.567 – 1.260	*NS*	0.869	0.644 – 1.182	*NS*	1.764	1.593 – 1.983	**
Chronic renal failure	0.949	0.569 – 1.571	*NS*	0.958	0.672 – 1.361	*NS*	1.073	0.808 – 1.424	*NS*
Ulcers	1.869	0.765 – 4.588	*NS*	1.840	0.903 – 3.735	*NS*	1.799	0.983 – 3.286	*NS*
Liver cirrhosis	1.511	0.519 – 4.385	*NS*	1.510	0.621 – 3.674	*NS*	1.040	0.428 – 2.512	*NS*
DM1	1.020	0.319 – 3.221	*NS*	0.939	0.386 – 2.268	*NS*	0.898	0.442 – 1.803	*NS*
DM2	0.905	0.669 – 1.217	*NS*	1.203	0.978 – 1.484	*NS*	1.128	0.947 – 1.338	*NS*
Sleep apnea	0.971	0.452 – 2.081	*NS*	1.004	0.569 – 1.758	*NS*	1.120	0.718 – 1.743	*NS*
Depression	0.686	0.452 – 1.039	*NS*	1.065	0.805 – 1.408	*NS*	1.161	0.929 – 1.447	*NS*
Anxiety	1.776	1.136 – 2.773	**	1.305	0.890 – 1.912	*NS*	1.530	1.145 – 2.047	**

Note.

* $p < 0.001$.

** $p < 0.05$.

All analyses were adjusted for age, gender and smoking status.

[a] All the groups with number of comorbidities are compared with the zero comorbidity group (reference group).

[b] The specific types of comorbidities are compared with not having the comorbidity.

Abbreviations: HR = hazard ratio. CI = 95% confidence interval. NS = not significant. Heart failure = chronic heart failure. CAD = coronary artery disease. AF = atrial fibrillation. AFL = atrial flutter. Ulcers = gastric or duodenal ulcers. DM1 = diabetes mellitus type 1. DM2 = diabetes mellitus type 2.

Types of comorbidities and readmission

As shown in Figure 4B, a log-rank test revealed a significant difference between cumulative readmission curves of patients with and without atrial fibrillation/atrial flutter and anxiety at 30-, 90- and 365-day follow-up (all *p*-values <0.001). Furthermore, patients with chronic heart failure, asthma and interstitial lung disease had significantly shorter readmission free survival time compared with patients without these comorbidities (all *p*-values <0.05).

The adjusted Cox proportional hazards analysis (Table 4B) showed that comorbidities associated with significantly increased 30-, 90- and 365-day all-cause readmission included atrial fibrillation/atrial flutter and interstitial lung disease (all *p*-values <0.05). Anxiety was a significant predictor of 30- and 365-day all-cause readmission (HR: 1.776, 95% CI: 1.136-2.773 and HR: 1.530, 95% CI: 1.145-2.047). Furthermore, asthma and lung cancer were associated with increased 365-day all-cause readmission (HR: 1.764, 95% CI: 1.593-1.983 and HR: 1.469, 95% CI: 1.094-1.999).

Mortality

Among all 1439 patients in the study population a total of 81 (5.6%) patients died within 30, 90 and 365 days, respectively, without having any readmission. As shown in Table 5A, having 1, 2-3 and ≥ 4 comorbidities was associated with significantly increased hazard of mortality after adjusting for age, gender and smoking status. Table 5B illustrates that lung cancer, interstitial lung disease, lymphoma/leukemia and chronic renal failure were also significant predictors of mortality.

Table 5A and 5B.

Adjusted hazard ratios with 95% confidence intervals testing associations between probability of 30-, 90- and 365-day mortality and number and types of comorbidities, respectively.

5A *Model A*	30 days HR	30 days CI (95%)	30 days *p*	90 days HR	90 days CI (95%)	90 days *p*	365 days HR	365 days CI (95%)	365 days *p*
Number [a]									
0	1.0			1.0			1.0		
1	2.271	1.051 – 4.909	**	2.653	1.130 – 6.235	**	2.580	1.372 – 4.863	**
2-3	3.694	1.764 – 7.720	*	2.416	1.003 – 5.804	**	1.901	0.962 – 3.758	*NS*
≥ 4	2.820	0.863 – 9.234	*NS*	5.207	1.629 – 16.66	**	4.274	1.608 – 11.33	**

5B *Model B*	30 days HR	30 days CI (95%)	30 days *p*	90 days HR	90 days CI (95%)	90 days *p*	365 days HR	365 days CI (95%)	365 days *p*
Type [b]									
Heart failure	1.326	0.652 – 2.691	*NS*	0.660	0.229 – 1.911	*NS*	0.507	0.196 – 1.312	*NS*
CAD	1.119	0.661 – 1.890	*NS*	1.704	0.938 – 3.098	*NS*	1.530	0.929 – 2.516	*NS*
AF / AFL	1.241	0.716 – 2.156	*NS*	0.487	0.213 – 1.110	*NS*	0.742	0.401 – 1.368	*NS*
Stroke	1.192	0.565 – 2.507	*NS*	0.434	0.104 – 1.798	*NS*	1.701	0.550 – 2.433	*NS*
Lymphoma / Leukemia	2.039	0.454 – 9.160	*NS*	5.255	1.214 – 22.73	**	4.351	1.310 – 14.46	**
Cancer	1.265	0.590 – 2.721	*NS*	1.688	0.725 – 3.923	*NS*	1.471	0.699 – 3.127	*NS*
Lung cancer	3.663	1.754 – 7.641	*	4.203	1.879 – 9.400	*	3.944	1.956 – 7.945	*
Interstitial lung disease	0.678	0.091– 4.992	*NS*	4.071	1.170 – 14.13	**	4.954	1.692 – 14.49	**
Asthma	1.0714	0.502 – 2.288	*NS*	1.837	0.805 – 4.182	*NS*	1.533	0.775 – 3.036	*NS*
Chronic renal failure	2.247	1.114 – 4.530	**	2.036	0.886 – 4.654	*NS*	1.581	0.722 – 3.439	*NS*
Ulcers	2.490	0.547 – 11.38	*NS*	NA	NA	*NS*	NA	NA	*NS*
Liver cirrhosis	NA	NA	*NS*	NA	NA	*NS*	4.160	0.558 – 31.21	*NS*
DM1	NA	NA	*NS*	NA	NA	*NS*	NA	NA	*NS*
DM2	1.105	0.619 – 1.972	*NS*	1.328	0.685 – 2.571	*NS*	0.925	0.450 – 1.714	*NS*
Sleep apnea	NA	NA	*NS*	2.531	0.579 – 11.05	*NS*	1.961	0.459 – 8.432	*NS*
Depression	1.012	0.429 – 2.400	*NS*	0.729	0.218 – 2.427	*NS*	1.140	0.511 – 2.552	*NS*
Anxiety	0.766	0.181 – 3.282	*NS*	0.640	0.088 – 4.957	*NS*	0.843	0.199 – 3.598	*NS*

Note.

* $p < 0.001$.

** $p < 0.05$.

All analyses were adjusted for age, gender and smoking status.

[a] All the groups with number of comorbidities are compared with the zero comorbidity group (reference group).

[b] The specific types of comorbidities are compared with not having the comorbidity.

Abbreviations: HR = hazard ratio. CI = 95% confidence interval. NA = not applicable. NS = not significant. Heart failure = chronic heart failure. CAD = coronary artery disease. AF = atrial fibrillation. AFL = atrial flutter. Ulcers = gastric or duodenal ulcers. DM1 = diabetes mellitus type 1. DM2 = diabetes mellitus type 2.

Comparison of model A (number of comorbidities) and model B (type of comorbidities)

As shown in Figure 5, all models predicting readmission had an AUC over 0.8 and were significant (all *p*-values < 0.001). For 30-, 90- and 365-day readmission, respectively, the AUCs for model A were higher than the AUCs for model B.

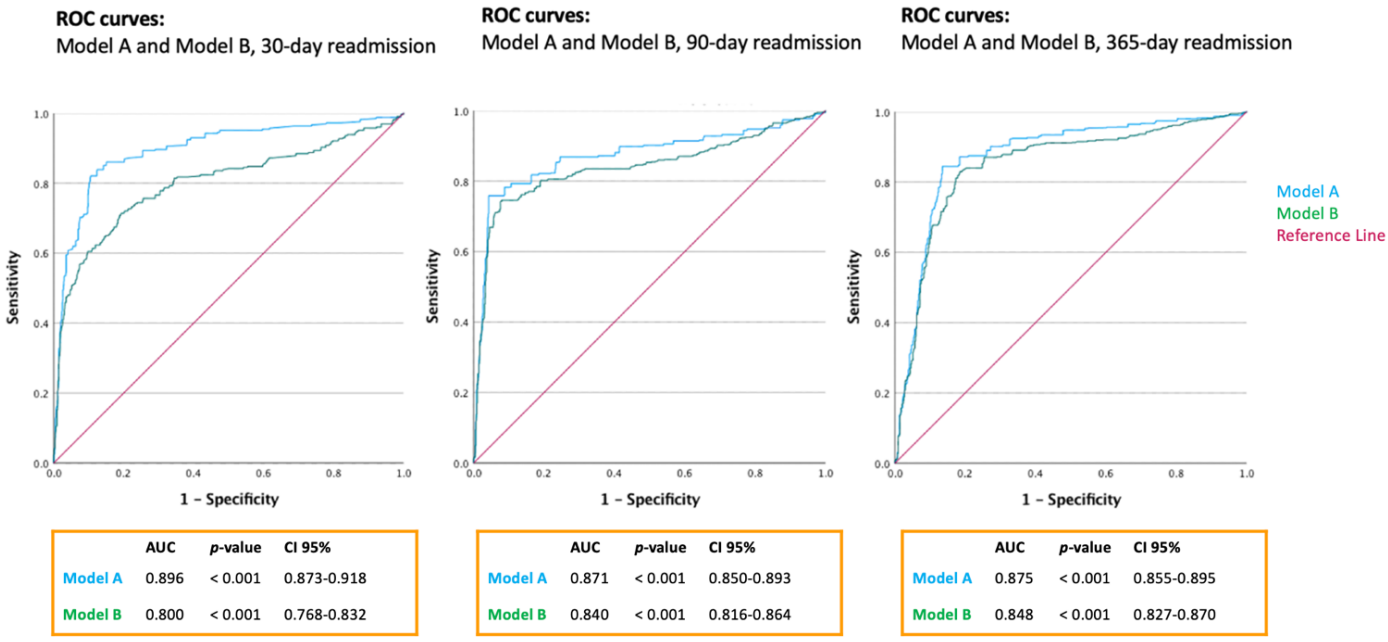

Figure 5. *Receiver operating characteristic curves and area under the ROC curves for hazard ratios for model A (number of comorbidities) and model B (type of comorbidities) predicting 30-, 90- and 365-day readmission.*

Note.
Abbreviations: ROC = receiver operating characteristic curves. AUC = area under the ROC curves. CI = 95% confidence interval.

Discussion

Interpretation of findings in relation to previously published studies

Results from this retrospective study provide valuable insight regarding risk factors associated with all-cause readmission in COPD patients. This study found that an increase in number of comorbidities and specific types of comorbidities including atrial fibrillation/ atrial flutter, lung cancer, interstitial lung disease, asthma and anxiety were generally associated with an increased risk of long-term readmission (i.e. 90 or 365 days). The only risk factors associated with short-term readmission (i.e. 30 days) were atrial fibrillation/ atrial flutter, interstitial lung disease and anxiety.
Furthermore, findings from this study indicate that the number of comorbidities is better at predicting 30, 90 and 365-day all-cause readmission compared to type of comorbidity.

Consistent with other studies' findings [28; 51], this study found that having ≥ 2 comorbidities generally increased all-cause 90-day readmission after a COPD index admission. This underlines even further that COPD patients with comorbidities are vulnerable.
Studies suggest that COPD-related readmissions in COPD patients in general are high 365 days after a COPD index admission [11; 52; 53]. However, these studies did not examine all-cause readmission rates more than 90 days after a COPD index admission. The present study indicates that readmission rates in multimorbid COPD patients remain high up to 365 days after an index admission. This adds new and important information to increase knowledge of COPD patients' trajectory after an index admission.

This study found no association between number of comorbidities and 30-day readmission. This is in contrast to previous studies [14; 20; 28]. These contradictions may be attributed to differences in selected comorbidities. This study included a larger number of comorbidities than other studies and was, as far as known, the only one including interstitial lung disease, depression and anxiety. Furthermore, one previous study only included veterans [20], which are a homogenous and special population compared to the general population [73; 74]. Thus, because of the differences in comorbidities and study population, no direct comparisons can be made between the findings in this study and the other studies.

Similarly to the present study's results, other studies found a significant association between increased 30-day readmission and atrial fibrillation/atrial flutter [21] and anxiety [54], respectively. Although lung cancer and asthma were significantly associated with 30- and 90-day all-cause readmission in this study, other studies found no association between these comorbidities and readmission [21; 28]. However, in this study, the confidence intervals for lung cancer were wide. Thus, there is an uncertainty on the effect size and the degree of

precision [55]. The wide confidence intervals can be due to the low number of individuals, and the results should therefore be interpreted with care.

This study found no significant association between readmission and chronic heart failure, cardiovascular diseases, renal failure and depression. This is inconsistent with other studies, which reported these comorbidities to be the most important risk factors for 30- and 90-day all-cause readmission in COPD patients [12; 21; 28; 32; 54; 56; 57]. There might be several possible explanations for the lack of association. For one, chronic renal failure was a risk factor for mortality. This makes mortality a potential competing risk and thus, it is conceivable that these patients died before having readmissions. Secondly, the inconsistency might be due, at least in part, to the differences in the study populations. In other studies, the average age for the 30-day and 90-day readmitted patients was between 57 and 69.12 years [28; 54; 56]. In this study, the 30- and 90-day readmitted patients were considerably older. In Denmark, COPD is commonly diagnosed at the age of 65 years on average [58], thus, this can explain why the patients in the present study were older than patients in other studies [28; 54; 56]. Research suggests that younger COPD patients may have similar pulmonary dysfunction as their older counterparts, but the pattern, prevalence and impact of comorbidities might be different [59-61]. Therefore, direct comparisons can not be made between this study's findings and previously published studies' findings. Lastly, in Denmark, all COPD patients as well as patients with other chronic diseases such as cardiovascular diseases and diabetes, are offered free follow-up care at their primary care physicians [62]. One study found that patients who had a follow-up visit after discharge had fewer hospital visits and lower readmission rates [63]. Thus, it is conceivable that the higher follow-up visits could explain why specific comorbidities, such as cardiovascular diseases, were not associated with increased readmission in this study.

Studies have shown that co-existent chronic diseases in COPD patients are often undiagnosed and poorly managed [64; 65]. Thus, there should be focused on addressing these conditions proactively to timely identify these and start readmission reduction efforts with the intention of increasing quality of life, reducing decline in lung function, decreasing mortality, and reducing healthcare costs [1; 66]. This study highlights the importance of identifying all comorbidities regardless of type rather than focusing on specific comorbidities which have been reported to have an association with increased readmission in COPD patients.

Strengths and limitations

The strengths of this retrospective cohort study include the large number of patients investigated and the setting. Denmark is a great setting for research studies due to the high reliability of the Danish medical registers, which are well established for a number of diagnoses [67], procedures [68] and vital status [69]. As state health care is free of charge in Denmark [40], it is guaranteed that all the patients included in this study had access to free health care, regardless of economic status. Furthermore, it was possible to identify all COPD patients with a COPD index admission in the North Denmark Region in 2018.

Another strength of this study is that index admission diagnoses were defined according to the validation study by Thomsen et al. [44]. Furthermore, to identify patients hospitalised with an index COPD admission, the patients' medical records for 2018 were manually screened for COPD admissions.

Lastly, to minimise misclassification, measure bias and interobserver variation, data was controlled and validated by another entry clerk uninvolved in this study. Thus, the database is considered reliable.

A limitation of this study is its retrospective design, as retrospective studies tend to have more missing data [70]. In general, missing values ≥ 10% are considered substantial [71]. However, in this study, the confounders adjusted for had < 10% missing data and thus, the risk of the results in this study being biased is low.

Several studies have found that an AECOPD increases the risk of getting a new AECOPD [40; 41]. However, the first COPD admission in 2018, defined as the index admission in this study, may not necessarily have been the first-ever AECOPD hospitalisation. Thus, the study population was a mix of patients who were at different stages in their disease progression, which may have systematically affected risks for readmission. However, only including patients with a first-ever AECOPD hospitalisation would possibly result in a significant loss of power, and thus, all patients with an AECOPD index admission in 2018 were included.

Conclusion

The results from this retrospective cohort study reported that having 2-3 and ≥4 comorbidities is associated with a significantly increased hazard of 90- and 365-day readmission in Danish COPD patients hospitalised with a COPD index admission.

Moreover, atrial fibrillation/ atrial flutter and interstitial lung disease are associated with 30, 90- and 365-day readmission. Besides lung cancer and asthma, anxiety is associated with 365-day readmission. Furthermore, anxiety is associated with 30-day readmission.

Lastly, the number of comorbidities is a better predictor of 30-, 90 and 365-day readmission than type of comorbidity.

References

1. Global Initiative for Chronic Obstructive Lung Disease (2022). *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2023 report.* Retrieved October 8, 2022 from: https://goldcopd.org/2023-gold-report-2/

2. Lindberg, A., Lindberg, L., Sawalha, S. et al. (2021). Large underreporting of COPD as cause of death-results from a population-based cohort study. *Respir Med. 186* (106518). https://doi.org/10.1016/j.rmed.2021.106518

3. World Health Organization (2020). *The top 10 causes of death*. Retrieved October 9, 2022 from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

4. Loncar, D. & Mathers, C.D. (2006). Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med. 3*(11), e442. https://doi.org/10.1371/journal.pmed.0030442

5. Finch, C.K., Guarascio, A.J., Ray, S.M., Self. T.H. (2013). The clinical and economic burden of chronic obstructive pulmonary disease in the USA. *Clinicoecon Outcomes Res. 5*, 235–245. https://doi.org/10.2147/CEOR.S34321

6. Global Burden of Disease Chronic Respiratory Disease Collaborators (2020). Prevalence and attributable health burden of chronic respiratory diseases, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Respir Med 8*(6), 585-596. http://doi.org/10.1016/S2213-2600(20)30105-3

7. Mathioudakis, A.G., Janssens, W., Sivapalan, P. et al. (2020). Acute exacerbations of chronic obstructive pulmonary disease: in search of diagnostic biomarkers and treatable traits. *Thorax, 75*(6), 520–527. https://doi.org/10.1136/thoraxjnl-2019-214484

8. Damianaki, A., Makris, D., Milic Emili, J., Moschandreas, J., Ntaoukakis, E., Siafakas, N.M., Tzanakis, N. (2007). Exacerbations and lung function decline in COPD: new insights in current and ex-smokers. *Respir Med. 101*(6), 1305-1312. https://doi.org/10.1016/j.rmed.2006.10.012

9. Hartl, S., Lopez-Campos, J.L., Pozo-Rodriguez, F., Castro-Acosta, A., Studnicka, M., Kaiser, B., Roberts, C.M. (2016). Risk of death and readmission of hospital-admitted COPD exacerbations: European COPD Audit. *Eur Respir J. 47*(1), 113-121. https://doi.org/10.1183/13993003.01391-2014

10. Lindenauer, P.K., Dharmarajan, K., Qin, L., Lin, Z., Gershon, A.S., Krumholz, H.M. (2018). Risk trajectories of readmission and death in the first year after hospitalization for chronic obstructive pulmonary disease. *Am J Respir Crit Care Med. 197*(8), 1009–1017. https://doi.org/10.1164/rccm.201709-1852OC

11. Njoku, C.M., Wimmer, B.C., Peterson, G.M., Kinsman, L., Bereznicki, B.J (2022). Hospital Readmission Due to Chronic Obstructive Pulmonary Disease: A Longitudinal Study. *Int J Health Policy Manag. 11*(11), 2533-2541. https://doi.org/10.34172/ijhpm.2022.5770

12. Alqahtani, J.S., Njoku, C.M., Bereznicki, B., Wimmer, B.C., Peterson, G.M., Kinsman, L., Aldabayan, Y.S., Alrajeh, A.M., Aldhahir, A.M., Mandal, S., Hurst, J.R. (2020). Risk factors for all-cause hospital readmission following exacerbation of COPD: a systematic review and meta-analysis. *Eur Respir Rev. 29*(156), 190166. https://doi.org/10.1183/16000617.0166-2019

13. Hurst J.R., Skolnik, N., Hansen, G.J., Anzueto, A., Donaldson, G.C., Dransfield, M.T., Varghese, P. (2020). Understanding the impact of chronic obstructive pulmonary disease exacerbations on patient health and quality of life. *Eur J Intern Med. 73*(1), 1-6. https://doi.org/10.1016/j.ejim.2019.12.014

14. Considine, J., Fox, K., Plunkett, D., Mecner, M., O Reilly, M., Darzins, P (2019). Factors associated with unplanned readmissions in a major Australian health service. *Aust Health Rev*. *43*(1), 1-9. https://doi.org/10.1071/AH16287

15. Jo, Y.S., Rhee, C.K., Kim, K.J., Yoo, K.H., Park, Y.B. (2020). Risk factors for early readmission after acute exacerbation of chronic obstructive pulmonary disease. *Ther Adv Respir Dis. 14*. https://doi.org/10.1177/1753466620961688

16. Kim, Y., Kim, Y.J., Cho, W.K. (2021). Effect of multiple comorbidities on mortality in chronic obstructive pulmonary disease among Korean population: a nationwide cohort study. *BMC Pulm Med. 21*(56). https://doi.org/10.1186/s12890-021-01424-7

17. Buhr, R.G., Jackson, N.J., Dubinett, S.M., Kominski, G.F., Mangione, C.M., Ong, M.K. (2020). Factors Associated with Differential Readmission Diagnoses Following Acute Exacerbations of Chronic Obstructive Pulmonary Disease. *J Hosp Med. 15*(4), 219-227. https://doi.org/10.12788/jhm.3367

18. Brunner-La Rocca, H.P., Peden, C.J., Soong, J., Holman, P.A., Bogdanovskaya, M., Barclay, L. (2020). Reasons for readmission after hospital discharge in patients with chronic diseases-Information from an international dataset. *PLoS One. 15*(6), e0233457. https://doi.org/10.1371/journal.pone.0233457

19. Jacobs, D.M., Noyes, K., Zhao, J., Gibson, W., Murphy, T.F., Sethi, S., Ochs-Balcom, H.M. (2018). Early Hospital Readmissions after an Acute Exacerbation of Chronic Obstructive Pulmonary Disease in the Nationwide Readmissions Database. *Ann Am Thorac Soc. 15*(7), 837-845. https://doi.org/10.1513/AnnalsATS.201712-913OC

20. Spece, L.J., Epler, E.M., Donovan, L.M., Griffith, M.F., Collins, M.P., Feemster, L.C., Au, D.H. (2018). Role of Comorbidities in Treatment and Outcomes after Chronic Obstructive Pulmonary Disease Exacerbations. *Ann Am Thorac Soc.* 15(9), 1033-1038. https://doi.org/10.1513/AnnalsATS.201804-255OC

21. Alpaydin, A.O., Ozuygur, S.S., Sahan, C., Tertemiz, K.C., Russell, R. (2021). 30-day Readmission After an Acute Exacerbation of Chronic Obstructive Pulmonary Disease is Associated with Cardiovascular Comorbidity. *Turk Thorac J. 22*(5), 369-375. https://doi.org/10.5152/TurkThoracJ.2021.0189

22. Hakim, M.A., Garden, F.L., Jennings, M.D., Dobler, C.C. (2017). Performance of the LACE index to predict 30-day hospital readmissions in patients with chronic obstructive pulmonary disease. *Clin Epidemiol. 10*, 51-59. https://doi.org/10.2147/CLEP.S149574

23. de Oca M.M. (2020). Smoking Cessation/Vaccinations. *Clin Chest Med. 41*(3), 495-512. doi: https://doi.org/10.1016/j.ccm.2020.06.013

24. Alqahtani, J.S., Aldabayan, Y.S., Aldhahir, A.M.,, Al Rajeh, A.M., Mandal, S., Hurst, J.R. (2021). Predictors of 30- and 90-Day COPD Exacerbation Readmission: A Prospective Cohort Study. *Int J Chron Obstruct Pulmon Dis. 16*, 2769-2781. https://doi.org/10.2147/COPD.S328030

25. Hurst, J.R., Han, M.K., Singh, B., Sharma, S., Kaur, G., de Nigris, E., Holmgren, U., Siddiqui, M.K. (2022). Prognostic risk factors for moderate-to-severe exacerbations in patients with chronic obstructive pulmonary disease: a systematic literature review. *Respir Res. 23*(1), 213. https://doi.org/10.1186/s12931-022-02123-5

26. Safford, M.M., Allison, J.J., Kiefe, C.I. (2007). Patient complexity: more than comorbidity. the vector model of complexity. *J Gen Intern Med*. *22*(3), 382-390. https://doi.org/10.1007/s11606-007-0307-0

27. Rinne, S.T., Graves, M.C., Bastian, L.A., Lindenauer, P.K., Wong, E.S., Hebert, P.L., Liu, C.F. (2017). Association between length of stay and readmission for COPD (2017). *Am J Manag Care*, 23(8), e253-e258.
Retrieved October 8, 2022 from: https://pubmed.ncbi.nlm.nih.gov/29087152/

28. Candrilli, S.D., Dhamane, A.D., Meyers, J.L., Kaila, S. (2015). Factors associated with inpatient readmission among managed care enrollees with COPD. *Hosp Pract (1995), 43*(4), 199-207. https://doi.org/10.1080/21548331.2015.1085797

29. Divo, M.J., Martinez, C.H., Mannino, D.M. (2014). Ageing and the epidemiology of multimorbidity. *Eur Respir J*. *44*(4), 1055-1068. https://doi.org/10.1183/09031936.00059814

30. Barnett, K., Mercer, S.W., Norbury, M., Watt, G., Wyke, S., Guthrie, B. (2012). Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet*. *380*(9836), 37-43. https://doi.org/10.1016/S0140-6736(12)60240-2

31. Adler, D., Cavalot, G., Brochard, L. (2020). Comorbidities and Readmissions in Survivors of Acute Hypercapnic Respiratory Failure. *Semin Respir Crit Care Med*. *41*(6), 806-816. https://doi.org/10.1055/s-0040-1710074

32. Schwab, P., Dhamane, A.D., Hopson, S.D., Moretz, C., Annavarapu, S., Burslem, K., Renda, A., Kaila, S. (2017). Impact of comorbid conditions in COPD patients on health care resource utilization and costs in a predominantly Medicare population. *Int J Chron Obstruct Pulmon Dis*. *23*(12), 735-744. https://doi.org/10.2147/COPD.S112256

33. Bahaadinbeigy, K., Yogesan, K., Wootton, R (2010). MEDLINE versus EMBASE and CINAHL for telemedicine searches. *Telemed J E Health, 16*, 916-919. https://doi.org/10.1089/tmj.2010.0046

34. Ahmadi, M., Ershad-Sarabi, R., Jamshidiorak, R., Bahaadinbeigy, K. (2014). Comparison of bibliographic databases in retrieving information on telemedicine. *J Kerman Univ Med Sci. 21*(4), 343-354.
Retrieved October 9, 2022 from: https://jkmu.kmu.ac.ir/article_16204.html

35. Considine, J., Shaban, R.Z., Fry, M., Curtis, K. (2017). Evidence based emergency nursing: designing a research question and searching the literature. *Int Emerg Nurs. 32*, 78–82. https://doi.org/10.1016/j.ienj.2017.02.001

36. Egghe, L. (2008). The measures precision, recall, fallout and miss as a function of the number of retrieved documents and their mutual interrelations. *Inform Proces Manag. 44*, 856-876. https://doi.org/10.1016/j.ipm.2007.03.014

37. Frandsen, T.F., Dyrvig, A-K., Christensen, J.B., Fasterholdt, I., Oelholm, A.M. (2014). En guide til valide og reproducerbare systematiske litteratursøgninger. *Ugeskr Læger, 176*, 647-651.
Retrieved October 8, 2022 from: https://ugeskriftet.dk/videnskab/V02130141

38. The EQUATOR (Enhancing the QUAlity and Transparency Of health Research) Network. *Reporting guidelines for main study types*.
Retrieved October 8, 2022 from: https://www.equator-network.org/

39. Region Nordjylland (2021). *Regioner i Danmark*. Retrieved October 28, 2022 from: https://rn.dk/genveje/fakta-om-nordjylland/regioner-i-danmark

40. Ehrenstein, V., Antonsen, S., Pedersen, L. (2010). Existing data sources for clinical epidemiology: Aarhus University Prescription Database. *Clin Epidemiol. 2*, 273-279. https://doi.org/10.2147/CLEP.S13458

41. Lynge, E., Sandegaard, J.L., Rebolj, M. (2011). The Danish National Patient Register. *Scand J Public Health, 39* (7 suppl), 30-33. https://doi.org/10.1177/1403494811401482

42. Pedersen, C.B. (2011). The Danish civil registration system. *Scand J Public Health 39* (7 Suppl), 22-25. https://doi.org/10.1177/1403494810387965

43. Hansen, S. K., Thorndahl, S. V., Weinreich, U. M. (2021). Protocol: EXAcerbations of COPD; Identification of risk factors for readmission EXAcise.
Retrieved September 8, 2022 from:

https://vbn.aau.dk/en/publications/protocol-exacerbations-of-copd-identification-of-riskfactors-for-

44. Thomsen, R.W., Lange, P., Hellquist, B., Frausing, E., Bartels, P.D., Krog, B.R., Hansen, A.M., Buck, D., Bunk, A.E. (2011). Validity and underrecording of diagnosis of COPD in the Danish National Patient Registry. *Respir Med. 105*(7), 1063-1068. https://doi.org/10.1016/j.rmed.2011.01.012

45. de Marco, R., Marcon, A., Rossi, A., Antó, J.M., Cerveri, I., Gislason, T., Heinrich, J., Janson, C., Jarvis, D., Kuenzli, N., Leynaert, B., Probst-Hensch, N., Svanes, C., Wjst, M., Burney, P. (2015). Asthma, COPD and overlap syndrome: a longitudinal study in young European adults. *Eur Respir J. 46*(3), 671-679. https://doi.org/10.1183/09031936.00008615

46. Guerra, S. (2009). Asthma and chronic obstructive pulmonary disease. Curr *Opin Allergy Clin Immunol. 9*(5), 409-416. https://doi.org/10.1097/ACI.0b013e3283300baf

47. D.G. Kleinbaum, M. Klein (2012). *Survival Analysis - A Self Learning Text* (3rd ed.). Springer-Verlag. https://doi.org/10.1007/978-1-4419-6646-9

48. Mandrekar, J.N. (2010). Receiver operating characteristic curve in diagnostic test assessment. *J Thorac Oncol. 5*(9), 1315-1316. https://doi.org/10.1097/JTO.0b013e3181ec173d

49. Metz, C.E. (1978). Basic principles of ROC analysis. *Semin Nucl Med. 8*(4), 283-298. https://doi.org/10.1016/s0001-2998(78)80014-2

50. Hosmer, D.W., Lemeshow, S. (2000). *Applied logistic regression* (2nd ed.). John Wiley and Sons.

51. Almagro, P., Cabrera, F.J., Diez, J., Boixeda, R., Ortiz, M.B.A., Murio, C., Soriano, J.B. (2012). Comorbidities and short-term prognosis in patients hospitalized for acute exacerbation of COPD: the EPOC en Servicios de medicina interna (ESMI) study. *Chest. 142*(5), 1126-1133. https://doi.org/10.1378/chest.11-2413

52. Tsui, M.S., Lun, F.C., Cheng, L.S., Cheung, A.P., Chan, V.L., Leung, W.S., Chu, C.M (2016). Risk factors for hospital readmission for COPD after implementation of the GOLD guidelines. *Int J Tuberc Lung Dis*. *20*(3), 396-401. https://doi.org/10.5588/ijtld.15.0256

53. Njoku, C.M., Alqahtani, J.S., Wimmer, B.C., Peterson, G.M., Kinsman, L., Hurst, J.R., Bereznicki, B.J. (2020). Risk factors and associated outcomes of hospital readmission in COPD: A systematic review. *Respir Med. 173*, 105988. https://doi.org/10.1016/j.rmed.2020.105988

54. Singh, G., Zhang, W., Kuo, Y.F., Sharma, G. (2016). Association of Psychological Disorders With 30-Day Readmission Rates in Patients With COPD. *Chest. 149*(4), 905-915. https://doi.org/10.1378/chest.15-0449

55. Hazra, A. (2017). Using the confidence interval confidently. *J Thorac Dis. 9*(10), 4125-4130. https://doi.org/10.21037/jtd.2017.09.14

56. Yu, T.C., Zhou, H., Suh, K., Arcona, S. (2015). Assessing the importance of predictors in unplanned hospital readmissions for chronic obstructive pulmonary disease. *Clinicoecon Outcomes Res. 7*, 37-51. https://doi.org/10.2147/CEOR.S74181

57. Baker, C.L., Zou, K.H., Su, J. (2013). Risk assessment of readmissions following an initial COPD-related hospitalization. *Int J Chron Obstruct Pulmon Dis. 8*, 551-559. https://doi.org/10.2147/COPD.S51507

58. Marinus, J. (2022). Lang fra alle KOL-patienter bliver opdaget hos deres praktiserende læge. *Sundhedspolitisk Tidsskrift.*
Retrieved November 22, 2022 from:
https://sundhedspolitisktidsskrift.dk/nyheder/sundhedspolitik/6948-langt-fra-alle-kol-patienter-bliver-opdaget-hos-deres-praktiserende-laege.html

59. Divo, M.J., Casanova, C., Marin, J.M., Pinto-Plata, V.M., de-Torres, J.P., Zulueta, J.J., Cabrera, C., Zagaceta, J., Sanchez-Salcedo, P., Berto, J., Davila, R.B., Alcaide, A.B., Cote, C., Celli, B.R., BODE Collaborative Group (2015). COPD comorbidities network. *Eur Respir J. 46*(3), 640-650. https://doi.org/10.1183/09031936.00171614

60. Vanfleteren, L.E., Spruit, M.A., Groenen, M., Gaffron, S., van Empel, V.P., Bruijnzeel, P.L., Rutten, E.P., Roodt, J.O,, Wouters, E.F., Franssen, F.M. (2013). Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med. 187*(7), 728-735. https://doi.org/10.1164/rccm.201209-1665OC

61. Vijayasaratha, K., Stockley, R.A. (2012). Relationship between frequency, length, and treatment outcome of exacerbations to baseline lung function and lung density in alpha-1 antitrypsin-deficient COPD. *Int J Chron Obstruct Pulmon Dis. 7*, 789-796. https://doi.org/10.2147/COPD.S31797

62. Friderichsen, B., Kristensen, J.K., Dam-Hansen, N. (2020). Overbliksstatus og årsstatus. *Dansk Selskab for Almen Medicin*.
Retrieved November 22, 2022 from:
https://vejledninger.dsam.dk/media/files/21/overbliksstatus-og-rsstatus.pdf

63. Sharma, G., Kuo, Y.F., Freeman, J.L., Zhang, D.D., Goodwin, J.S. (2010). Outpatient follow-up visit and 30-day emergency department visit and readmission in patients hospitalized for chronic obstructive pulmonary disease. *Arch Intern Med. 170*(18), 1664-1670. https://doi.org/10.1001/archinternmed.2010.345

64. Skou, S.T., Mair, F.S.,, Fortin, M., Guthrie, B., Nunes, B.P., Miranda, J.J., Boyd, C.M., Pati, S., Mtenga, S., Smith, S.M. (2022). Multimorbidity. *Nat Rev Dis Primers. 8*(1), 48. https://doi.org/10.1038/s41572-022-00376-4

65. Burke H., Wilkinson, T.M.A. (2021). Unravelling the mechanisms driving multimorbidity in COPD to develop holistic approaches to patient-centred care. *Eur Respir Rev. 30*(160), 210041. https://doi.org/10.1183/16000617.0041-2021

66. National Institute for Health and Care Excellence (2016). Multimorbidity: clinical assessment and management; NICE guideline [NG56]. Published date: 21 September 2016. Retrieved October 22, 2022 from: https://www.nice.org.uk/guidance/ng56

67. Thygesen, S.K., Christiansen, C.F., Christensen, S., Lash, T.L., Sørensen, H.T. (2011). The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol*. *11*(1), 83. https://doi.org/10.1186/1471-2288-11-83

68. Blichert-Hansen, L., Nielsson, M.S., Nielsen, R.B., Christiansen, C.F., Nørgaard, M. (2013). Validity of the coding for intensive care admission, mechanical ventilation, and acute dialysis in the Danish National Patient Registry: a short report. *Clin Epidemiol. 5*(1), 9–12. https://doi.org/10.2147/CLEP.S37763

69. Schmidt M., Pedersen, L., Sørensen, H.T. (2014). The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. *29*(8), 541–549. https://doi.org/10.1007/s10654-014-9930-3

70. Altman D.G., Bland, J.M. (2007). Missing data. *BMJ, 334*(7590), 424. https://doi.org/10.1136/bmj.38977.682025.2C

71. Bennet, D. A. (2001). How can I deal with missing data in my study? *Aust N Z J Public Health. 25*(5), 464-469. Retrieved October 22, 2022 from: https://pubmed.ncbi.nlm.nih.gov/11688629/

72. Lykkegaard, J. (2021). Årlig kontrol som kvalitetsmål. *Ugeskr. Læger 183*(6). Retrieved November 22, 2022 from: https://ugeskriftet.dk/videnskab/arligkontrolsomkvalitetsmal

73. Morgan, R.O., Teal, C.R., Reddy, S.G., Ford, M.E., Ashton, C.M. (2005). Measurement in Veterans Affairs Health Services Research: veterans as a special population. *Health Serv Res. 40*(5 Pt 2), 1573-83. https://doi.org/10.1111/j.1475-6773.2005.00448.x

74. Olenick, M., Flowers, M., Diaz, V.J. (2015). US veterans and their unique issues: enhancing health care professional awareness. *Adv Med Educ Pract. 6*, 635-9. https://doi.org/10.2147/AMEP.S89479