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an observational cohort study of 22.053 patients

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Original article

Pseudomonas aeruginosa and risk of death and exacerbations in patients with chronic obstructive pulmonary disease: an observational cohort study of 22 053 patients

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A R T I C L E   I N F O

A B S T R A C T

Objectives: The role of *Pseudomonas aeruginosa* in the long-term prognosis of chronic obstructive pulmonary disease (COPD) is unknown. The purpose of this study was to determine whether *P. aeruginosa* is associated with increased risk of exacerbations or death in patients with COPD.
Methods: This is a multiregional epidemiological study based on complete data on COPD outpatients between 1 January 2010 and 31 October 2017 and corresponding microbiology and national register data. Time-dependent Cox proportional hazards models and propensity matching was used to estimate hospitalization-demanding exacerbations and death after 2 years, separately and in combination.
Results: A total of 22 053 COPD outpatients were followed for a median of 1082 days (interquartile-range: 427—1862). *P. aeruginosa* was present in 905 (4.1%) patients. During 730 days of follow-up, *P. aeruginosa* strongly and independently predicted an increased risk of hospitalization for exacerbation or all-cause death (HR 2.8, 95%CI 2.2—3.6; p <0.0001) and all-cause death (HR 2.7, 95%CI 2.3—3.4; p <0.0001) in analyses adjusted for known and suspected confounders. The signal remained unchanged in unadjusted analyses as well as propensity-matched subgroup analyses. Among patients 'ever colonized' with *P. aeruginosa,* the incidence of hospital-demanding exacerbations doubled after the time of the first colonization.
Conclusions: COPD patients in whom *P. aeruginosa* can be cultured from the airways had a markedly increased risk of exacerbations and death. It is still not clear whether this risk can be reduced by offering patients targeted antipseudomonal antibiotics. A randomized trial is currently recruiting patients to clarify this (ClinicalTrials.gov: NCT03262142). **J. Eklöf, Clin Microbiol Infect 2020;26:227**

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Introduction

According to the Global Burden of Disease Study, 3.2 million people died from chronic obstructive pulmonary disease (COPD) in 2017 [1], and the burden of the disease continues to grow [2]. A large part of the burden of COPD is associated with recurrent exacerbation events which impair health status and worsen the prognosis [3].

Pseudomonas aeruginosa has been reported to be present in the airways in 4–20% of patients with acute exacerbation of COPD [4–7]. Although the evidence is sparse and the methodology variable, it has been suggested that *P. aeruginosa* is associated with prolonged hospitalization, increased exacerbation rate and poor long-term prognosis in COPD patients [8–10]. However, no definitive conclusions regarding the clinical impact of *P. aeruginosa* in COPD patients can be made since the bacterium is seen primarily in advanced disease [6,11], which is in itself a strong predictor for poor prognosis [12].

Thus, the aim of the current study was to evaluate whether *P. aeruginosa* is independently associated with long-term adverse outcomes in COPD patients. To address this, we conducted a multiregional observational study with complete follow-up on the investigated endpoints, and we performed multivariate regression analyses and propensity score matching.

Methods

Study design

This was a multiregional cohort study of COPD outpatients with and without *P. aeruginosa* cultured from the lower respiratory tract.

Data sources

Data from nationwide and regional administrative registries in accordance with current Danish laws (Data Protection Agency: 2012-58-0004; The Danish National Committee on Health Research Ethics: H-15010949). According to these laws, informed consent is not required for registry-based studies. Linkage between registries was done by using unique personal identification numbers, which allows an exact linkage on individual level and ensures complete follow-up [13].

Data were retrieved from the nationwide Danish Register of Chronic Obstructive Pulmonary Disease (DrCOPD). The DrCOPD holds individual data on all outpatient visits and hospital admissions due to exacerbation of COPD, in patients aged 30 years or above, at all Danish hospitals since 2008. Fig. 1 displays the inclusion process. All patients who were registered with a visit to the outpatient clinic between 1 January 2010 and 31 October 2017 in the DrCOPD were included. Patients with malignant neoplasms within 5 years prior to study entry were excluded since this condition is strongly associated with mortality and may affect the ability to interpret the results of the study exposure. (Supplementary Table S1 lists the International Classification of Disease 10th revision (ICD-10) codes used to define malignant neoplasms.)

DrCOPD data were linked with microbiology data from the Clinical Microbiology Departments in Eastern Denmark (Region Zealand and Capital Region), with approximately 2.6 million inhabitants. We defined the study population as COPD outpatients with any microbiological data. All patients from Eastern Denmark were included, regardless of microbiological status. Patients from the western part of Denmark were not included since we could not gain access to microbiological data for these patients. Study entry day was defined as the date for the patients first visit to the outpatient clinic in the DrCOPD.

Patient characteristics

Patient characteristics were assessed at study entry. Information was obtained from the DrCOPD and the Danish National Patient Registry (DNPR). The DNPR holds data on all Danish in-hospital and out-patient-clinic contacts since 1977 (Supplementary Table S2 lists the ICD-10 codes used to define comorbidities).

Pseudomonas aeruginosa status

Exposure was defined as any *P. aeruginosa*-positive culture sample from the lower respiratory tract (i.e. sputum, tracheal secretion, bronchial secretion and bronchial alveolar lavage) after the study participant's entry date in the DrCOPD until end of follow-up on 31 October 2017. Exposure date was defined as the date of the first registered positive sample.

Outcome measures

The primary outcomes of this study were (a) combined endpoint of hospitalization for exacerbation or all-cause death, and (b) all-cause death separately, respectively, after 2 years.

A secondary analysis was performed to estimate the separate outcome of hospitalization for exacerbation after 2 years using a competing risk model (Supplementary Table S7).

We chose to assess outcome after 2 years since we expected a general low long-term survival rate in the study population based on previous national [14] and international literature [15] on mortality in COPD. Data on outcomes were retrieved from the DrCOPD and DNPR. ICD-10 codes used to define exacerbation are listed in Supplementary Table S3.

Statistical methods

A time-dependent Cox proportional hazard regression model was developed to assess the risk between *P. aeruginosa* and outcome. *P. aeruginosa* was included as a time-dependent variable, taking time period as exposed within the first 2 years from study entry into account. Change in status from unexposed to exposed could only occur once, at the time for exposure date, and remained unchanged during the remaining follow-up time. The Cox model was adjusted for known and suspected cofounders assessed at study entry based on previous literature in the field: age (continuous), sex (male versus female), severity of airflow obstruction based on percentage predicted forced expiratory volume in the first second; forced expiratory volume (FEV_1) (ordinal: 1–4), medical research council dyspnoea scale (MRC) (ordinal: 1-5), body mass index (BMI) (continuous), smoking status (active versus not active), previous hospitalization for exacerbation of COPD within 12 months prior to study entry (yes versus no), inhaled corticosteroid; ICS (yes versus no) and calendar year for entry in DrCOPD (ordinal: 2010–2017). Patients with unknown smoking status were classified as non-active smokers. No forward or backward variable selection was made. The models were tested for linearity of continuous variables, proportion of hazards and interactions and found to be valid.

A greedy-matched propensity score model [16] was applied as a sensitivity analysis, forming a subpopulation of patients with available microbiological data on culture samples from the lower respiratory tract. The model used algorithms created and maintained by biomedical statisticians at the Mayo Clinic [17]. Patients with *P. aeruginosa*-positive samples were matched (1:5 ratio) with
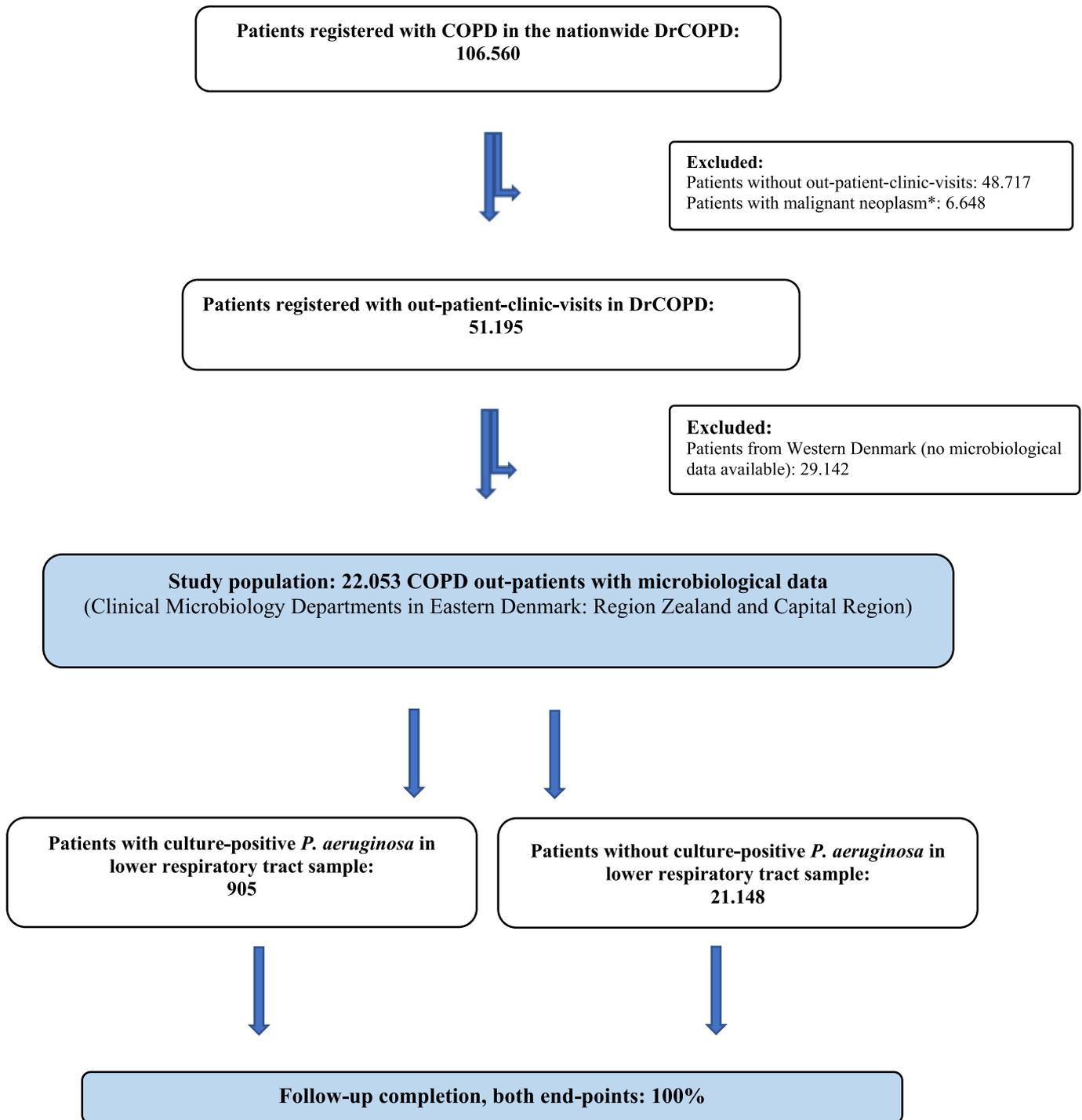
Fig. 1. Selection of study population: 22 053 patients registered with chronic obstructive pulmonary disease (COPD) in the Danish Register of Chronic Obstructive Pulmonary Disease (DrCOPD) between 1 January 2010 and 31 October 2017.

patients who had never-positive-*P. aeruginosa* lower respiratory tract samples using calendar year for study entry and the probability of being exposed to *P. aeruginosa* based on characteristics at study entry: i.e. age, sex, FEV_1% predicted, MRC, BMI, inhaled corticosteroids (ICS), smoking status and previous hospitalization for exacerbation. In patients with unknown FEV_1% predicted, MRC and BMI at study entry, measurements from the first following outpatient clinic visit were used. In the propensity matched population, the risk estimates of *P. aeruginosa* were calculated by comparing

outcomes between the two matched groups by using a univariate Cox proportional hazard model (i.e. *Pseudomonas* status: positive versus negative). Sample date were set as exposure date in both groups. The estimate was retested using a robust variance estimator, accounting for the lack of independence in outcomes induced by the matching.

A second propensity score model, inverse probability of treatment weighting (IPTW) of propensity score [16], was additionally performed as a sensitivity analysis (Supplementary Table S6A-C).

Cox proportional hazard regression models are presented as hazard ratios (HRs) with 95% confidence intervals (95%CIs). Cumulative incidence plots are used to illustrate the cumulative probability of exacerbation and death. Continuous variables are presented as median values and interquartile ranges. Group comparisons were performed using non-parametric test (Wilcoxon two-sample test) and t-test when appropriate. Categorical variables are reported as frequencies and proportions and compared between groups using Fisher's exact test. A p $\leq$0.05 was considered statistically significant. Statistical analyses were performed using SAS statistical software 9.4 (SAS Institute Inc., Cary, NC, USA) and statistical software R (version 3.4.3).

Results

A total of 22 053 COPD outpatients were identified in the DrCOPD between 1 January 2010 and 31 October 2017 (Fig. 1). Patients were followed for 1082 days (interquartile range: 427—1862). The number of patients with *P. aeruginosa* was 905 (4.1%). Table 1 displays the characteristics of patients who were *P. aeruginosa*-positive and *P. aeruginosa*-negative during the study period at the time for inclusion into the study. The two groups were similar overall, except for clinically relevant differences in lung function capacity, frequency of hospital-demanding exacerbation for COPD prior to study entry, prescribed corticosteroid inhalation medicine and concurrent diagnoses of asthma and bronchiectasis. Follow-up completion for study outcomes were 100% in both groups. Time to

initial *P. aeruginosa*-positive sample was 649 days (interquartile-range: 216—1278).

Outcomes

Hospitalization for exacerbation or all-causes death (94% versus 48%, p <0.0001) and all-cause death separately (41% versus 17%, p <0.0001) after 2 years occurred more frequently in *P. aeruginosa*-positive patients than in patients without *P. aeruginosa*. *P. aeruginosa* was associated with a significantly increased risk of both outcomes in unadjusted analyses (HR 3.7, 95%CI 3.0—4.6, p <0.0001 and HR 5.1, 95%CI 4.4—5.8, p <0.0001 respectively) and the risk remained large and significant in the multivariable analyses (Table 2). Fig. 2 illustrates the cumulative incidence.

In the *P. aeruginosa*-positive patients, the incidence rate of hospital-demanding exacerbations substantially increased after the first isolation of *P. aeruginosa* compared to before the isolation of the bacterium (Fig. 3).

Sensitivity analyses

A subgroup of 4679 patients with COPD were analysed in the propensity matched model. This group consisted of 798 *P. aeruginosa*-positive patients (17%) matched 1:5 with 3881 patients (83%) with lower respiratory tract samples never positive for *P. aeruginosa* (Supplementary Fig. S1). Patient characteristics of the two groups are presented in Supplementary Table S4.

Table 1
Characteristics of the patients at study entry and by exposure to *Pseudomonas aeruginosa* at any time during the study period (1 January 2010 to 31 October 2017)

	All patients	COPD patients with *P. aeruginosa*	COPD patients without *P. aeruginosa*	p-value
	$n = 22\ 053$ (100%)	$n = 905$ (4.1%)	$n = 21.148$ (95.9%)	
Demographics				
Age, median (IQR)	69 (62—76)	71 (65—76)	69 (62—76)	<0.0001
Male, *n* (%)	9.868 (44.8)	407 (45.0)	9.461 (44.7)	0.891
MRC, median (IQR)	3 (2—4)	3 (3—4)	3 (2—4)	<0.0001
Unknown MRC, *n* (%)	4.823 (21.9)	173 (19.1)	4.650 (22.0)	
FEV$_1$% predicted, median (IQR)	49 (36—63)	39 (29—50)	49 (37—63)	<0.0001
Unknown FEV$_1$%, *n* (%)	4.462 (20.2)	166 (18.3)	4.296 (20.3)	
BMI, median (IQR)	25 (21—29)	23 (20—27)	25 (21—29)	<0.0001
Unknown BMI, *n* (%)	4.704 (23.2)	171 (18.9)	4.533 (21.2)	
Smoking status, *n* (%):				<0.0001
Active	6.729 (30.5)	242 (26.7)	6.487 (30.7)	
Former ($\leq$ 6 months)	599 (2.7)	10 (1.1)	589 (2.8)	
Former (> 6 months)	9.694 (44.0)	470 (51.9)	9.224 (43.6)	
Never	594 (2.7)	21 (2.3)	573 (2.7)	
Unknown	4.437 (20.1)	162 (17.9)	4.275 (20.2)	
Prescribed inhalation therapy, *n* (%):				
Inhaled corticosteroids	15.851 (71.9)	823 (90.9)	15.028 (71.1)	<0.0001
Inhaled long-acting β$_2$-agonist or long-acting muscarin antagonist	18.315 (83.0)	864 (95.5)	17.451 (82.5)	<0.0001
Hospitalization for exacerbation of COPD 12 months prior to study entry, *n* (%):	11.492 (52.1)	598 (66.1)	10.894 (51.5)	<0.0001
Comorbidity, *n* (%):				
Immunodeficiency	130 (0.59)	9 (0.99)	121 (0.57)	0.115
Inflammatory polyarthropathy	674 (3.1)	16 (1.8)	658 (3.1)	0.018
Systemic connective tissue disorder	566 (2.5)	30 (3.3)	536 (2.6)	0.161
Myocardial infarction	1.711 (7.7)	77 (8.5)	1.634 (7.8)	0.375
Atrial fibrillation	3.205 (14.5)	134 (14.8)	3.071 (14.5)	0.810
Heart failure	3.607 (16.4)	147 (16.2)	3.460 (16.4)	0.963
Hypertension	6.856 (31.2)	273 (30.2)	6.583 (31.1)	0.558
Renal failure	960 (4.4)	38 (4.2)	922 (4.4)	0.934
Peripheral vascular disease	1.754 (8.0)	66 (7.3)	1.688 (8.0)	0.490
Cerebrovascular disease	2.099 (9.5)	77 (8.5)	2.022 (9.6)	0.325
Diabetes mellitus, type 2	2.654 (12.1)	106 (11.7)	2.548 (12.0)	0.794
Asthma	3.216 (14.6)	187 (20.7)	3.029 (14.3)	<0.0001
Bronchiectasis	249 (1.1)	36 (4.0)	213 (1.0)	<0.0001

IQR, interquartile range; MRC, Medical Research Council dyspnoea scale; BMI, body mass index (kg/m^2); FEV$_1$, forced expiratory volume in the first second.

Table 2
Cox regression hazard estimates for hospital-demanding exacerbation and all-cause death after 2 years with *Pseudomonas aeruginosa* as time-dependent variable

Hospitalization for exacerbation of COPD or all-cause death	Unadjusted HR (95%CI)	p-value	Adjusted HR (95%CI)	p-value
P. aeruginosa-positive	3.7 (3.0–4.6)	<0.0001	2.8 (2.2–3.6)	<0.0001
Hospitalization for exacerbation of COPD 12 months prior to study entry	2.1 (2.1–2.2)	<0.0001	1.7 (1.7–1.8)	<0.0001
MRC	1.5 (1.5–1.6)	<0.0001	1.4 (1.3–1.4)	<0.0001
Inhaled corticosteroid	1.6 (1.5–1.7)	<0.0001	1.2 (1.2–1.3)	<0.0001
Active smoking	1.0 (1.0–1.1)	0.730	1.2 (1.2–1.3)	<0.0001
Age (per year)	1.03 (1.03–1.03)	<0.0001	1.02 (1.02–1.02)	<0.0001
Male	0.9 (0.9–1.0)	0.002	1.0 (1.0–1.0)	0.702
BMI (per unit increase)	0.98 (0.98–0.98)	<0.0001	1.00 (0.99–1.00)	0.074
FEV$_1$% predicted[a]	0.8 (0.8–0.8)	<0.0001	0.8 (0.8–0.9)	<0.0001
All-cause death	**Unadjusted HR (95%CI)**	**P-value**	**Adjusted HR (95%CI)**	**P-value**
P. aeruginosa-positive	5.1 (4.4–5.8)	<0.0001	2.7 (2.3–3.4)	<0.0001
Hospitalization for exacerbation of COPD 12 months prior to study entry	2.3 (2.2–2.5)	<0.0001	1.6 (1.5–1.8)	<0.0001
MRC	1.9 (1.9–2.0)	<0.0001	1.6 (1.6–1.7)	<0.0001
Active smoking	0.9 (0.8–0.9)	<0.0001	1.4 (1.3–1.5)	<0.0001
Male	1.0 (1.0–1.1)	0.175	1.2 (1.1–1.3)	<0.0001
Age (per year)	1.07 (1.06–1.07)	<0.0001	1.06 (1.05–1.06)	<0.0001
BMI (per unit increase)	0.95 (0.94–0.95)	<0.0001	0.97 (0.97–0.98)	<0.0001
Inhaled corticosteroid	1.4 (1.3–1.5)	<0.0001	0.8 (0.7–0.9)	0.0007
FEV$_1$% predicted[a]	0.7 (0.6–0.7)	<0.0001	0.7 (0.7–0.8)	<0.0001

Sensitivity analysis: Cox regression hazard estimates for hospital-demanding exacerbation and all-cause death after 2 years with Pseudomonas aeruginosa as time-dependent variable after excluding 249 patients with bronchiectasis.

Hospitalization for exacerbation of COPD or all-cause death	Unadjusted HR (95%CI)	p-value	Adjusted HR (95%CI)	p-value
P. aeruginosa-positive	3.3 (2.7–4.2)	<0.0001	2.5 (1.9–3.3)	<0.0001
All-cause death				
P. aeruginosa-positive	5.2 (4.5–6.0)	<0.0001	2.9 (2.4–3.5)	<0.0001

MRC, Medical Research Council dyspnoea scale; BMI, body mass index; FEV$_1$, forced expiratory volume in the first second.
The model is adjusted for calendar year for study entry and all variables displayed in the table.
Categorical variables are reported with one decimal place. Continuous variables are reported with two decimals.
[a] Increase in severity stage (1–4) of FEV$_1$% predicted defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).

P. aeruginosa-positive patients experienced significantly higher rates of both hospitalization for exacerbation or all-cause death (89% versus 77%, p <0.0001) and all-cause death separately (47% versus 37%, p <0.0001), and they had a numerically higher incidence of exacerbations compared to *P. aeruginosa*-negative patients (Supplementary Table S5). Although the estimates were somewhat reduced, *P. aeruginosa* remained strongly and significantly associated with both study outcomes (HR 1.7, 95%CI 1.5–1.8, p <0.0001 and HR 1.4, 95%CI 1.3–1.6, p <0.0001 respectively). Supplementary Fig. S2 illustrates the cumulative incidence. The outcome signal remained unchanged in the inverse probability of treatment weighting (IPTW) propensity score model (Supplementary Table S6A-C).

Lastly, the estimates for hospital-demanding exacerbation remained high in the competing risk analysis in the main cohort population (adjusted HR 2.7, 95%CI 2.1–3.5, p <0.0001) and propensity score subgroups (Supplementary Table S7).

Discussion

In this multiregional long-term follow-up epidemiological study of COPD outpatients, we found a low prevalence of *P. aeruginosa*. Patients with *P. aeruginosa* were substantially more likely to be hospitalized for exacerbation of COPD or die of all causes compared to those who never had this bacterial pathogen. Moreover, among the patients who had *P. aeruginosa* isolated at any time, there was a substantial increase in the incidence rate of hospital-demanding exacerbations after the first isolation of *P. aeruginosa* compared to before isolation of this bacterium. The result was robust for adjustment for several known and suspected confounders and was confirmed in propensity score sensitivity analyses using two different models.

To our knowledge, this study is the largest study ever to investigate the prevalence of *P. aeruginosa* and the clinical implications of colonization with this bacterium in an unselected population of COPD patients. Additionally, as compared with other research in this field, the current study is the first to report complete long-term follow-up on explored outcomes via nationwide registries.

Previous studies have primarily reported on smaller groups of patients, and the risk of selection bias and information bias may have been higher [4–11,18]. The prevalence of *P. aeruginosa* in our study is considerable lower than that in most of these previous studies [4,7,8], with reports of *P. aeruginosa* in up to 20% of the patients [8]. Our study was performed using complete data from the entire Eastern Denmark population during nearly 8 years.

Our finding that patients colonized with *P. aeruginosa* had poor outcome is consistent with that of Almagro et al. [10], who found *P. aeruginosa* to be an independent prognostic marker of 3-year mortality in a prospective study of 181 patients hospitalized with COPD exacerbation. In contrast, Boutou et al. [18] reported no association between *P. aeruginosa* and long-term survival in COPD outpatients in a smaller study (*n* = 132); power issues may, at least in part, explain that negative finding. Colonization with *P. aeruginosa* plays an important role in the course of other chronic lung diseases, in particular cystic fibrosis [19]. *P. aeruginosa* is also associated with poor outcomes in patients with bronchiectasis, in whom colonization with this bacterium has been reported to be increased three-fold [20].

The completeness of data in the current study is a major strength, allowing us to report long-term follow-up with high accuracy in a well-characterized, large and unselected group of patients. Additionally, the diagnoses used for acute COPD exacerbation and several of the comorbidities in the study have been validated with high positive predictive values in the DNPR (>90%) [21]. Moreover, use of robust and multiple acknowledged statistical models, adjusting for important prognostic predictors, further strengthens the internal data validity.
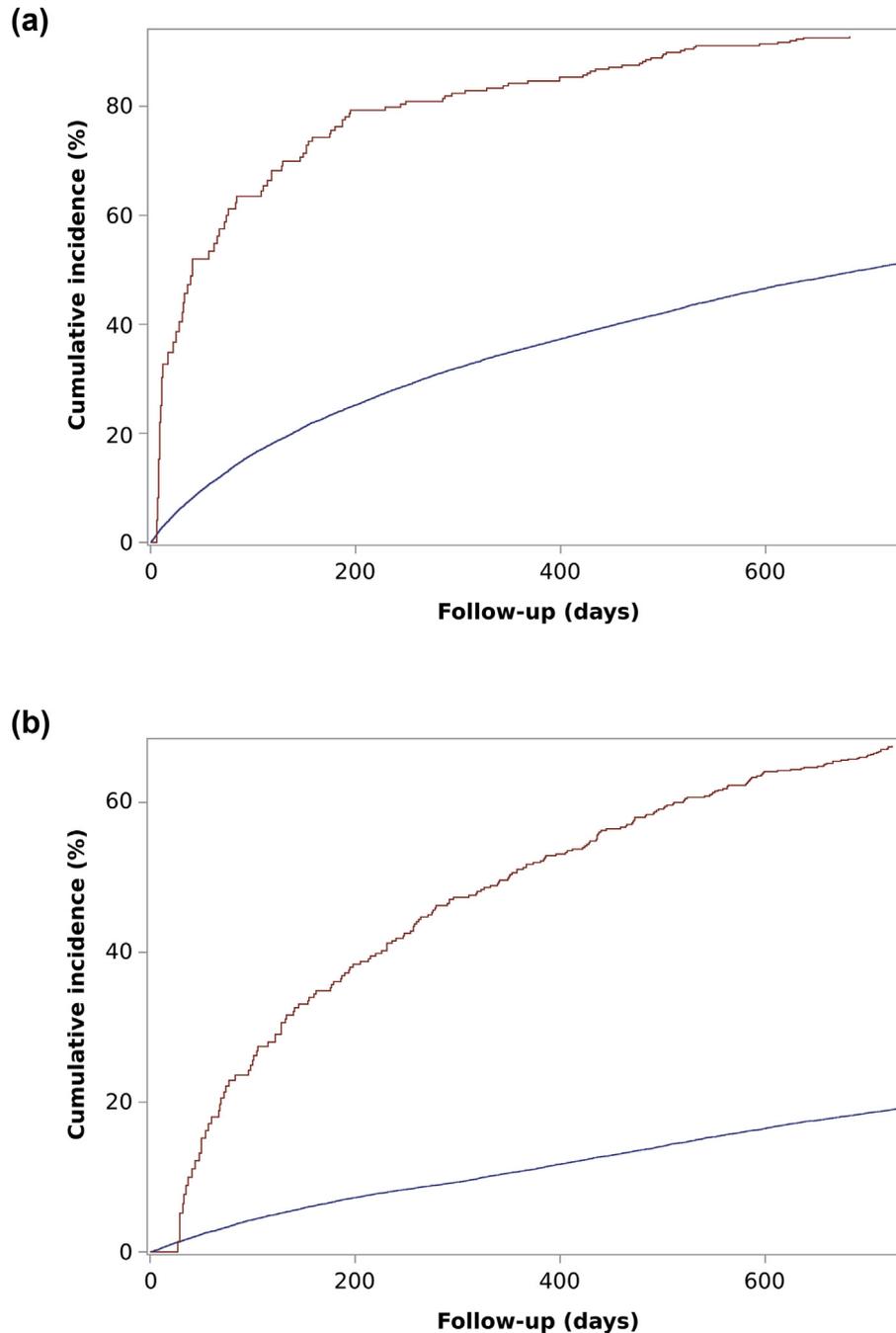
Fig. 2. Cumulative incidences of study outcomes. A. Hospitalization for exacerbation or all-cause death after 2 years. B. All-cause death after 2 years (red line: *Pseudomonas aeruginosa*-positive patients, blue line: *Pseudomonas aeruginosa*-negative patients).

Nevertheless, no definitive conclusions regarding causality can be drawn based on our data due to the observational design. Moreover, we hold no data on antibiotic utilization in the population. Thus, it is impossible to account fully for other possible unknown confounders that could have affected the results. However, the large study size and multiregional design makes the results most likely to be generalizable to other COPD outpatients inside and outside Denmark with similar COPD characteristics.

Patients were included in the study based on the diagnosis of COPD and any available microbiological data. Thus, *P. aeruginosa*-positive patients could possibly be compared to patients where respiratory cultures never were performed. This could be

considered a limitation. However, the patients entered the study at their first visit to the outpatient clinic, prior to and independently of possible respiratory samples in both groups. Furthermore, our propensity score sensitivity analyses were based on a subgroup of patients where data on respiratory cultures were available.

We chose not to control for comorbidities since the major diseases were evenly distributed between the groups. The slight difference in concurrent asthma was controlled for by adjusting for ICS in both the main and the sensitivity analyses. ICS was seen to be strongly correlated to exacerbations. This is not surprising since ICS is associated with increased risk of pneumonia and is reserved for patients with more severe disease [22]. However, ICS
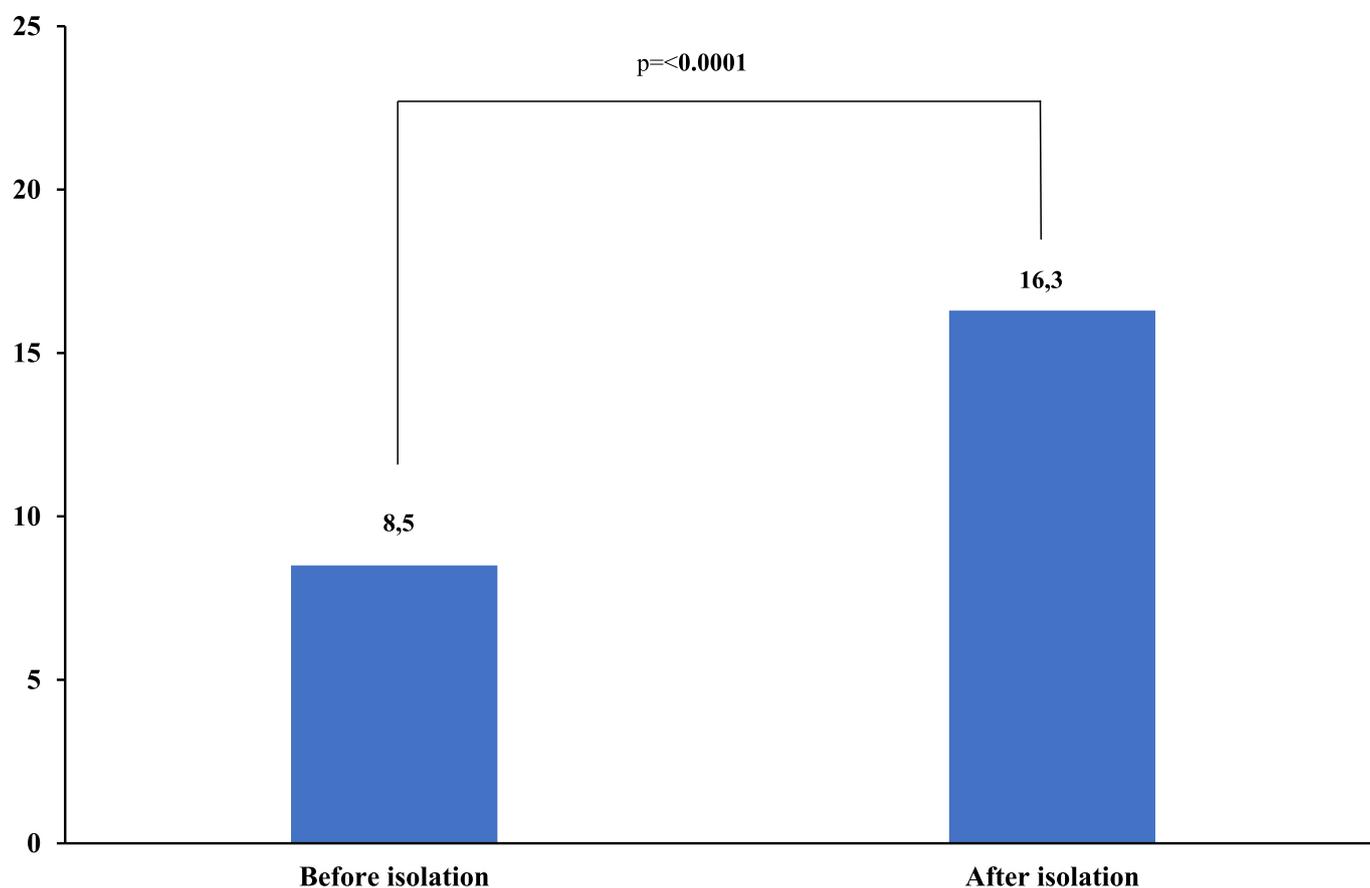
Fig. 3. Incidence of hospital-demanding exacerbation in 905 *Pseudomonas aeruginosa*-positive patients before and after isolation of *P. aeruginosa* (event/1000 days).

use did not appear to affect mortality. Few patients in our population had bronchiectasis. As a sensitivity analysis, we ran the main regression model while excluding these and this did not alter the signal.

The study addresses the prognostic role of *P. aeruginosa* in COPD, and it reveals that this infrequent bacterium has a substantial association with key outcomes, including exacerbations and mortality. Our study was not designed to address the mechanism associated with these unwanted events. However, possible theories include enhancement of airway inflammation, resulting in susceptibility to exacerbations and accelerated loss of lung function [23–25]. *P. aeruginosa* is a well-established contributor to irreversible decline in lung function in cystic fibrosis, and the pathogenesis is closely linked to well-studied and complex virulence mechanisms, including a high genetic flexibility and biofilm formation [19,26,27].

In conclusion, the long-term outcome, both in regard to death and hospital-demanding exacerbations, was substantially worse in those COPD patients colonized with *P. aeruginosa*. Further research is needed to give a deeper understanding of the mechanism behind these adverse clinical outcomes. And, most importantly, trial data are needed to determine whether targeted *Pseudomonas*-active antibiotic interventions can improve the prognosis in this highly vulnerable group of patients. A randomized trial is currently recruiting patients to clarify this (ClinicalTrials.gov: NCT03262142).

Transparency declaration

Author contributions

JE and JSJ contributed to the conception and design of the study, data collection and analysis, data interpretation, and writing the manuscript. RS and TSI contributed to the conception and design of the study, data analysis, data interpretation, and revision of the manuscript. PS contributed to the conception and design of the study, data collection and analysis and revision of the manuscript. IA contributed to data analysis and revision of the manuscript. JBB, JB, CO, RBD and USJ contributed to data collection and revision of the manuscript. AB, TSL, JJ, UMW, KA, TW and NS contributed to conception and design of the study and revision of the manuscript. All authors have approved the final manuscript and agreed to be accountable for all aspects of the work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2019.06.011.

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