Respiratory Medicine 155 (2019) 141–147

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Prognosis of COPD depends on severity of exacerbation history: A population-based analysis

Yunus Çolak[a,b,c], Shoaib Afzal[a,b,c], Jacob L. Marott[b], Børge G. Nordestgaard[a,b,c], Jørgen Vestbo[d], Truls S. Ingebrigtsen[b,e], Peter Lange[b,c,f,g,*]

[a] Department of Clinical Biochemistry, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark
[b] The Copenhagen General Population Study, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, and the Copenhagen City Heart Study, Bispebjerg and Frederiksberg Hospital, Copenhagen University Hospital, Copenhagen, Denmark
[c] Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[d] Division of Infection, Immunity and Respiratory Medicine, School of Biological Sciences, Manchester Academic Health Science Centre, University of Manchester, And Manchester University NHS Foundation Trust, Manchester, United Kingdom
[e] Medical Unit, Respiratory Section, Hvidovre Hospital, Copenhagen University Hospital, Hvidovre, Denmark
[f] Department of Public Health, Section of Epidemiology, University of Copenhagen, Copenhagen, Denmark
[g] Department of Internal Medicine, Section of Respiratory Medicine, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark

ARTICLE INFO

Keywords:
Airway obstruction
Spirometry
Forced expiratory volume
Chronic bronchitis
Emphysema

ABSTRACT

Background: Differences in previous exacerbation history may influence prognosis of chronic obstructive pulmonary disease (COPD). We hypothesized that prognosis differs between individuals with a history of only medically treated exacerbations (moderate exacerbations) and those with a history of hospitalised exacerbations (severe exacerbations).

Methods: We included 98 614 adults from the Copenhagen General Population Study and assessed risk of moderate and severe exacerbations, pneumonia hospitalisation, and respiratory and all-cause mortality from 2003 until 2013 according to exacerbation history.

Results: Among 6545 individuals with COPD, 6290 had no exacerbations in the preceding year, 109 had one moderate exacerbation, 108 had two or more moderate exacerbations, and 38 had one or more severe exacerbations. During 9.4 years of follow-up, we observed 926 moderate and 244 severe exacerbations, 477 pneumonias, and 707 deaths, including 69 from respiratory disease. Compared to individuals without previous exacerbations, lung function and symptom adjusted hazard ratios (HRs) for future moderate exacerbation were 4.68 (95% confidence interval:3.31–6.62) for individuals with one previous moderate exacerbation, 21 (13–33) for individuals with two or more previous moderate exacerbations, and 5.30 (3.44–8.15) for individuals with one or more previous severe exacerbations. Corresponding HRs were 1.62(0.78–3.34), 1.29(0.57–2.89), and 5.43 (2.56–12) for severe exacerbation, 1.86(1.06–3.27), 1.74(1.01–2.99), and 4.85 (2.94–8.02) for pneumonia, 0.53(0.10–2.99), 1.65(0.53–5.17), and 2.98 (1.14–7.83) for respiratory mortality, and 1.34(0.79–2.29), 1.57(1.00–2.47), and 1.49 (0.85–2.62) for all-cause mortality, respectively.

Conclusion: Individuals with COPD and a history of hospitalised exacerbations carried the poorest prognosis compared to those with a history of only medically treated exacerbations, suggesting difference in risk profile.

1. Introduction

Exacerbations, defined as acute worsening of symptoms, are common and severe complications of chronic obstructive pulmonary disease (COPD) leading to additional therapy and hospitalisations [1]. Since exacerbations significantly impact health status and accelerate disease progression, one of the important treatment goals in COPD is to reduce the risk and severity of future exacerbations [2]. The most recent recommendation of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) suggests that an exacerbation history with at least two mild or moderate exacerbations or at least one severe exacerbation leading to hospitalisation in the preceding year can be used to identify high-risk patients for future exacerbations and preventive treatment [1]. However, mild or moderate exacerbations are usually handled in

* Corresponding author. Professor, Consultant in Respiratory Medicine, Department of Public Health, Section of Epidemiology, University of Copenhagen, Øster Farimagsgade 5, Postal Box 2099, DK-1014, Copenhagen K, Denmark.
E-mail address: peter.lange@sund.ku.dk (P. Lange).

https://doi.org/10.1016/j.rmed.2019.07.021
Received 24 May 2019; Received in revised form 22 July 2019; Accepted 24 July 2019
Available online 25 July 2019
0954-6111/

general practice and may not require extensive additional therapy, whereas severe exacerbations require hospitalisation and are often associated with increased mortality [3].

We investigated risk of future moderate and severe exacerbations, pneumonia hospitalisation, and respiratory and all-cause mortality in individuals with COPD from the general population according to exacerbation history in the preceding year. We hypothesized that prognosis differs between individuals with a history of only medically treated exacerbations (moderate exacerbations) and those with a history of hospitalised exacerbations (severe exacerbations).

2. Methods

2.1. Study population

We recruited 98 614 individuals aged 20–100 years from the Copenhagen General Population Study, a Danish contemporary population-based cohort study initiated in November 26, 2003 with ongoing enrolment [4,5]. All participants provided written informed consent, completed a comprehensive questionnaire, and underwent a physical examination. Questionnaires were reviewed at the day of attendance by a healthcare professional together with the participant. The study was approved by Herlev and Gentofte Hospital and the regional ethics committee (approval number: H-KF-01-144/01), and was conducted according to the Declaration of Helsinki.

2.2. COPD and exacerbation history

Lung function was determined using spirometry with pre-bronchodilator measurements of forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) [6]. COPD was defined as $FEV_1/FVC < 0.70$ in former and current smokers aged ≥40 years with cumulative tobacco consumption ≥10 pack-years and without asthma (Fig. 1). Asthma diagnosis was based on self-report or a previous hospital contact due to asthma (International Classification of Diseases [ICD]-8: 493 and ICD-10: J45-J46), as obtained from the national Danish Patient Registry, which records all public and private hospital contacts in Denmark. Information on exacerbation history in the preceding year was obtained from two sources. Moderate exacerbations were defined as treatment with oral corticosteroid alone or in combination with antibiotics (Anatomical Therapeutic Chemical [ATC] Classification System: H02AB), obtained from the national Danish Registry of Medicinal Product Statistics, which records all prescriptions dispensed in pharmacies in Denmark [7]. Severe exacerbations (ICD-10: J41-J44) were defined as acute emergency department visit and/or hospitalisation with the mentioned primary diagnosis, obtained from the national Danish Patient Registry [4]. Individuals with COPD were subsequently assigned into one of four mutually exclusive subgroups (Fig. 1):

1) No exacerbations: individuals without moderate or severe exacerbations in the preceding year.
2) One moderate exacerbation: individuals with only a single moderate exacerbation in the preceding year and no severe exacerbation.
3) Two or more moderate exacerbations: individuals with at least two moderate exacerbations in the preceding year and no severe exacerbation.
4) One or more severe exacerbations: individuals with at least one severe exacerbation in the preceding year irrespective of number of moderate exacerbations.

2.3. Outcomes

Moderate exacerbations were defined as treatment with oral corticosteroid alone or in combination with antibiotics (ATC Classification System: H02AB), obtained from the national Danish Registry of Medicinal Product Statistics, recorded until April 23, 2013. Severe exacerbations (ICD-10: J41-J44) and pneumonias (ICD-10: J12-J18) were defined as acute emergency department visit and/or hospitalisation with the mentioned primary diagnosis, obtained from the national Danish Patient Registry, recorded until April 10, 2013. Information on

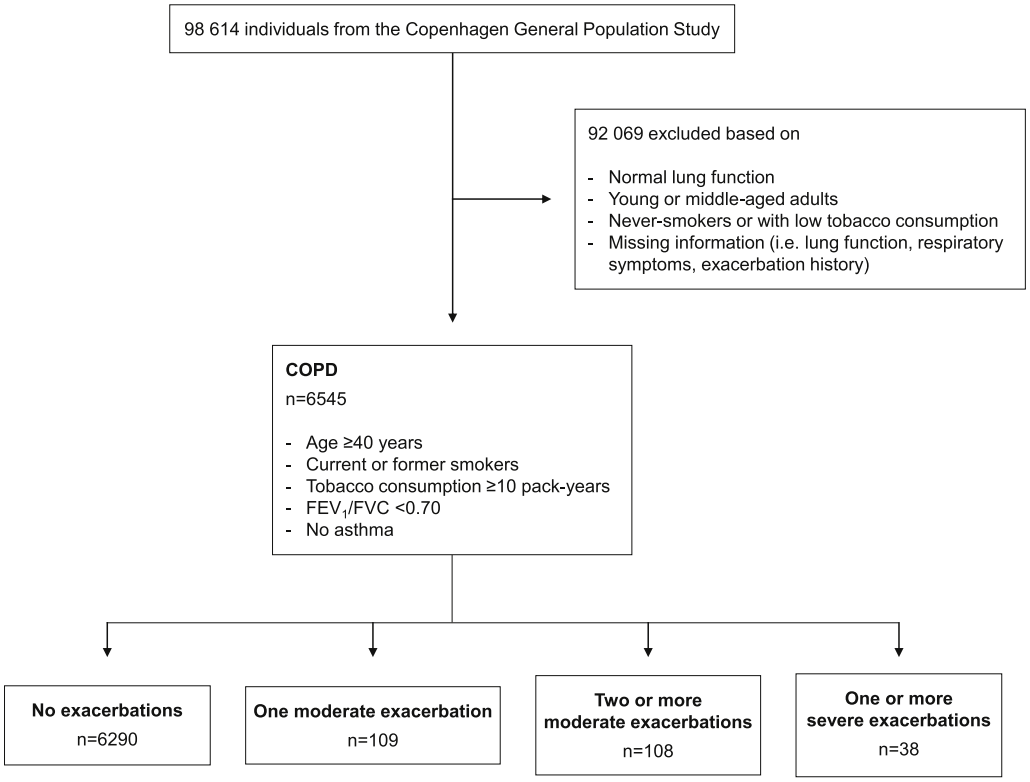

Fig. 1. Flowchart. COPD = chronic obstructive pulmonary disease. FVC = forced vital capacity.

vital status was obtained from the national Danish Civil Registration System, which contains date of death for all individuals resident in Denmark, recorded until April 23, 2013. Information on cause of death was obtained from the national Danish Causes of Death Registry, which contains date and causes of death for all individuals resident in Denmark, recorded until December 30, 2011. Death due to respiratory disease (ICD-10: J00-J99) was based on the underlying cause of death. Since the national Danish Causes of Death Registry lags the national Danish Civil Registration System by approximately one year, not all deaths could be classified by cause.

2.4. Statistical analyses

Wilcoxon's rank-sum, Pearson's χ^2, or Fischer's exact tests were used for comparisons. Cox regression analysis was used to determine time to first event. Fine & Gray competing risk analysis [8] with the competing events being all-cause mortality and emigration was used to determine cumulative incidences for exacerbation, pneumonia, and respiratory mortality and Kaplan-Meier analysis was used to determine cumulative incidence for all-cause mortality. Generalised linear model analysis using pseudo-observations for the restricted or conditional mean event time under right-censoring according to the methods proposed by Andersen, Hansen, and Klein [9] was used to determine mean survival time during follow-up, corresponding to approximately 10 years. Analyses were carried out crude and adjusted for various predictors of COPD prognosis, including FEV_1 stage (FEV_1 $\geq$80% predicted, 50–79%, 30–50%, and < 30% predicted), modified Medical Research Council dyspnoea scale (mMRC) score (< versus $\geq$2), age, sex, civil status, smoking status, cumulative tobacco consumption in pack-years, previous hospitalisation due to pneumonia and ischemic heart disease, and treatment with airway medication (no versus yes). Effect modification of age and living alone on risk of outcomes was investigated using likelihood-ratio test. Analyses were carried out using STATA/SE 13.1.

3. Results

Among all 98 614 participants, 6545 had COPD, of whom 6290 (96%) had no exacerbations in the preceding year, 109 (1.6%) had one moderate exacerbation, 108 (1.6%) had two or more moderate exacerbations, and 38 (0.6%) had one or more severe exacerbations (Fig. 1). Among all individuals with FEV_1 < 50% of the predicted value, more than 13% exacerbated in the preceding year. Individuals with exacerbations in the preceding year compared to those without had lower lung function, were more often symptomatic, and in treatment with airway medication (Table 1). During a median follow-up time of 3.8 years (range up to 9.4 years), we observed 926 moderate and 244 severe exacerbations, 477 pneumonias, and 707 deaths, of which 69 were due to respiratory disease.

3.1. Future exacerbations

Cumulative incidence for moderate exacerbation was highest in individuals with two or more moderate exacerbations in the preceding year, followed by individuals with one or more severe exacerbation, individuals with one moderate exacerbation, and individuals without exacerbation (Fig. 2). Cumulative incidence for severe exacerbation was highest in individuals with a history of severe exacerbation in the preceding year. Within the first year of follow-up, cumulative incidences for any exacerbation were 63% in individuals with two or more moderate exacerbations, 31% in individuals with one or more severe exacerbations, 22% in individuals with one moderate exacerbation, and 3.9% in individuals with no exacerbation in the preceding year.

Compared to individuals without exacerbation in the preceding year, crude hazard ratios (HRs) for moderate exacerbation were 6.54 (95% confidence interval [CI]: 4.72–9.06) for individuals with one previous moderate exacerbation, 28 (19–41) for individuals with two or more previous moderate exacerbations, and 9.83 (6.18–16) for individuals with one or more previous severe exacerbations (Fig. 3). Corresponding HRs were 3.94 (2.09–7.42), 2.70 (1.30–5.61), and 22 (13–40) for severe exacerbation, and 6.57 (4.74–9.10), 27 (18–40), and 9.96 (6.20–16) for any exacerbation, respectively. After adjustment for various predictors of COPD prognosis (predominantly FEV_1 stage and mMRC score), risk estimates were slightly attenuated but similar for moderate and any exacerbation, whereas the 95% CIs for HRs for severe exacerbation overlapped 1.0 in individuals with a moderate exacerbation history, but not in individuals with a severe exacerbation history. Effect modification with age was only present for individuals with one previous moderate exacerbation on risk of any exacerbation and implicated a higher risk with increasing age (P-value for interaction from likelihood-ratio test = 0.03). We did not observe any effect modification with living alone on exacerbation risk.

Interestingly, only 29% of individuals with at least one severe exacerbation in the preceding year exacerbated after 1-year of follow-up and 37% after 2-years of follow-up (Fig. 4). Corresponding numbers were 13% and 36% in individuals with two or more moderate exacerbations in the preceding year, 10% and 17% in individuals with one moderate exacerbation, and < 1% and 2% in individuals without exacerbation, respectively.

3.2. Pneumonia and death

Individuals with a history of severe exacerbation experienced the highest incidences for pneumonia and respiratory mortality compared to the other three groups (Fig. 2). Furthermore, individuals with only one moderate exacerbation in the preceding year seemed to have similar incidences for pneumonia and respiratory mortality as those with two or more moderate exacerbations. Compared to the group without previous exacerbation, all groups with any form of exacerbation in the preceding year had higher and somewhat comparable incidences for all-cause mortality over the first five years of follow-up. Following the initial five years of observations, individuals with a history of severe exacerbation experienced a rapid increase in all-cause mortality surpassing individuals with a history of moderate exacerbations only.

Compared to individuals without exacerbation in the preceding year, crude HRs for pneumonia were 2.62 (95% CI: 1.53–4.49) for individuals with one previous moderate exacerbation, 2.72 (1.64–4.50) for individuals with two or more previous moderate exacerbations, and 9.73 (5.69–17) for individuals with one or more previous severe exacerbations (Fig. 5). Corresponding HRs were 1.27 (0.18–9.09), 3.27 (1.03–10), and 16 (7.55–36) for respiratory mortality, and 1.81 (1.09–3.01), 2.15 (1.40–3.32), and 3.18 (1.92–5.28) for all-cause mortality, respectively. Mean survival time was 8.80 years (95% CI: 8.71–8.88) for individuals without an exacerbation history in the preceding year, 8.18 years (7.49–8.87) for individuals with one moderate exacerbation, 7.72 years (6.91–8.53) for individuals with at least two moderate exacerbations, and 5.93 years (4.04–7.83) for individuals with at least one severe exacerbation (Fig. 5). After adjustment for FEV_1 stage and mMRC score, individuals with a history of moderate exacerbations only had an increased risk for pneumonia, whereas individuals with a history of severe exacerbation had an increased risk for pneumonia and respiratory mortality. Effect modification with age was only present for individuals with at least two moderate exacerbations on risk of respiratory mortality showing a lower risk with increasing age (P-value for interaction from likelihood-ratio test = 0.03). There was no effect modification with living alone on the risk of pneumonia, or respiratory or all-cause mortality.

4. Discussion

In this large Danish contemporary population-based cohort study,

Table 1
Characteristics of 6545 individuals with COPD according to exacerbation history in the preceding year in the Copenhagen General Population Study.

Characteristics	Exacerbation history			
	No exacerbations (n = 6290)	One moderate exacerbation (n = 109)	Two or more moderate exacerbations (n = 108)	One or more severe exacerbation (n = 38)
At baseline examination				
Age – years	66.0 (58.7–73.3)	68.8 (61.5–73.9)	72.3 (66.6–80.1)[a]	73.7 (65.2–78.2)[a]
Men – no. (%)	3608 (57)	57 (52)	55 (51)	20 (53)
Civil status				
Married/cohabitant – no. (%)	4300 (68)	79 (72)	68 (63)	22 (58)
Single – no. (%)	368 (5.9)	4 (3.7)	4 (3.7)	< 3 (5.3)
Separated/divorced – no. (%)	791 (13)	9 (8.3)	10 (9.3)	5 (13)
Widow/widower – no. (%)	816 (13)	17 (16)	26 (24)[a]	9 (24)
Unknown – no. (%)	15 (< 1)	0 (0)	0 (0)	0 (0)
Current smokers – no. (%)	2690 (43)	40 (37)	34 (31)[b]	10 (26)[b]
Cumulative tobacco consumption – pack-years	16.0 (12.9–20.0)	17.0 (12.9–21.0)	15.9 (12.8–23.6)	17.1 (14.0–19.5)
Previous pneumonia hospitalisation – no. (%)	53 (< 1)	0 (0)	7 (6.5)[b]	11 (29)[b]
Previous ischemic heart disease hospitalisation – no. (%)	66 (1)	0 (0)	0 (0)	3 (7.9)[b]
FEV_1 predicted – %	79 (66–91)	69 (55–83)[a]	71 (51–83)[a]	50 (41–63)[a]
FVC predicted – %	96 (83–109)	86 (69–100)[a]	85 (70–98)[a]	71 (59–81)[a]
FEV_1/FVC	0.65 (0.61–0.68)	0.63 (0.55–0.67)[b]	0.62 (0.55–0.67)[a]	0.54 (0.47–0.62)[a]
FEV_1% predicted < 50 – no. (%)	442 (7.0)	26 (24)[a]	23 (21)[a]	19 (50)[a]
FEV_1/FVC < LLN – no. (%)	5185 (82)	94 (86)	83 (77)	33 (87)
mMRC ≥2 – no. (%)	1134 (18)	41 (38)[a]	43 (40)[a]	26 (68)[a]
Treatment with airway medication – no. (%)	585 (9.3)	40 (37)[a]	29 (27)[a]	36 (95)[a]
SABA and/or SAMA – no. (%)	277 (4.4)	28 (26)[a]	21 (19)[a]	23 (61)[a]
ICS and LABA – no. (%)	280 (4.5)	27 (25)[a]	13 (12)[a]	23 (61)[a]
LABA – no. (%)	96 (1.5)	< 3 (< 2.8)	7 (6.5)[a]	5 (13)[a]
LAMA – no. (%)	202 (3.2)	18 (17)[a]	14 (13)[a]	21 (55)[a]
During follow-up				
Moderate exacerbations – no. (%)	762 (12)	50 (46)[a]	89 (82)[a]	25 (66)[a]
Severe exacerbations – no. (%)	207 (3.3)	11 (10)[a]	8 (7.4)[b]	18 (47)[a]
Any exacerbations[c] – no. (%)	780 (12)	51 (47)[a]	88 (81)[a]	25 (66)[a]
Pneumonias – no. (%)	428 (6.8)	15 (14)[a]	17 (16)[b]	17 (45)[b]
Respiratory deaths – no. (%)	59 (< 1)	< 3 (< 2.8)	3 (2.8)	6 (16)[a]
Deaths – no. (%)	656 (10)	16 (15)	22 (20)[a]	13 (34)[a]

Data presented as median (25th and 75th percentiles) or n (%). COPD = chronic obstructive pulmonary disease. FVC = forced vital capacity. ICS = inhaled corticosteroid. LABA = long-acting beta-2 agonist. LAMA = long-acting muscarinic antagonist. mMRC = modified Medical Research Council dyspnoea scale. SABA = short-acting beta-2 agonist. SAMA = short-acting muscarinic antagonist.

[a] $P < 0.001$.

[b] $P < 0.05$ for comparison with individuals with COPD but no exacerbation history.

[c] Due to differences in follow-up time between moderate and severe exacerbations, the number of any exacerbations may not add up.

we investigated risk of future moderate and severe exacerbations, pneumonia hospitalisation, and respiratory and all-cause mortality in individuals with COPD according to frequency and severity of exacerbation history in the preceding year. We found that COPD prognosis is highly dependent on the severity of a previous exacerbation history. Individuals with a history of severe exacerbation experienced the poorest prognosis and had a different risk profile compared to individuals with a history of moderate exacerbations only.

In 2011, GOLD revolutionised initial assessment of patients with COPD by introducing exacerbation history to the classification system, as FEV_1 stage lacked sufficient precision to determine the risk for future exacerbations [10]. A large part of the evidence behind this decision was based on results from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study, an observational cohort study of approximately 2000 extensively phenotyped COPD patients with moderate to severe disease followed for three years [11]. In ECLIPSE, exacerbation history was superior for predicting future exacerbations compared to other markers of COPD, including lung function impairment. Thus, an exacerbation history with at least two mild or moderate exacerbations in the preceding year or one severe exacerbation leading to hospitalisation was suggested by GOLD to identify patients with high risk for future exacerbations and thus candidates for preventive treatment [10]. With the recent update, GOLD has maintained this recommendation for treatment of naïve patients [1]. In the present study by using a population-based approach, we confirm that individuals with an exacerbation in the preceding year irrespective of frequency had an increased risk of future exacerbation. In addition, we observed that the severity of previous exacerbation seems to have a large impact on severity of future exacerbations and other respiratory outcomes. Individuals with a severe exacerbation history had more severe exacerbations and less frequently moderate in the following years, whereas the opposite was observed in individuals with only a moderate exacerbation history. History of previous severe exacerbation was also associated with increased respiratory mortality, despite taking lung function impairment and symptoms into account. There may be several explanations for these findings. Severe exacerbations can be associated with respiratory failure and require ventilatory support, and may therefore have a greater impact on COPD prognosis [3]. Indeed, severe exacerbations in COPD have been associated with accelerated lung function decline [12–16] and increased risk of mortality [14,17–23]. On the other hand, even a mild exacerbation in a stable COPD patient with severe lung function impairment may require a hospitalisation. Therefore, a hospitalisation due to an exacerbation may indicate presence of more advanced disease (Table 1) [24]. Thus, a history of severe exacerbation should be viewed differently than a history of moderate exacerbations only, which GOLD also takes into account by recommending that preventive treatment should be instituted immediately after one severe exacerbation.

Only 29% of individuals with a severe exacerbation history and 13% of individuals with an exacerbation history of at least two moderate exacerbations exacerbated after 1-year follow-up (Fig. 4). Thus, these groups, often denoted as frequent exacerbators based on the results

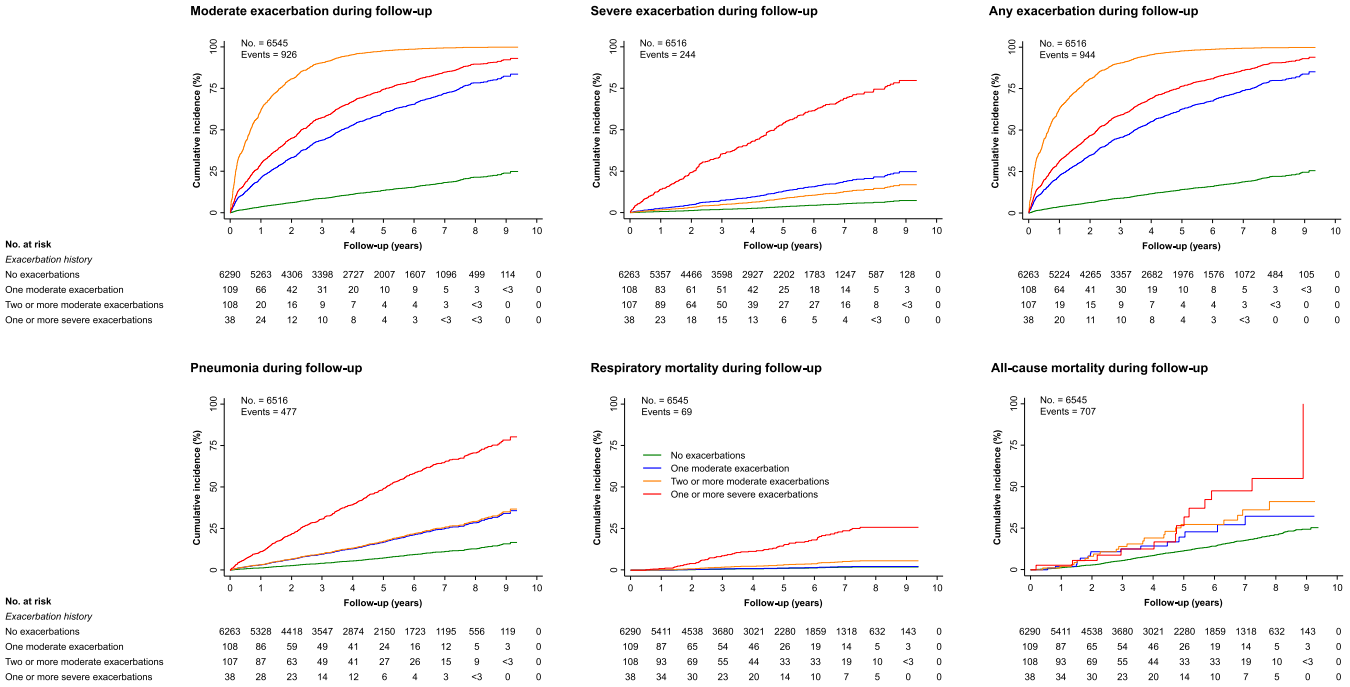

Fig. 2. Cumulative incidence for moderate and severe exacerbations, pneumonia, respiratory mortality, and all-cause mortality in individuals with COPD according to exacerbation history in the preceding year. Analyses are crude. COPD = chronic obstructive pulmonary disease.

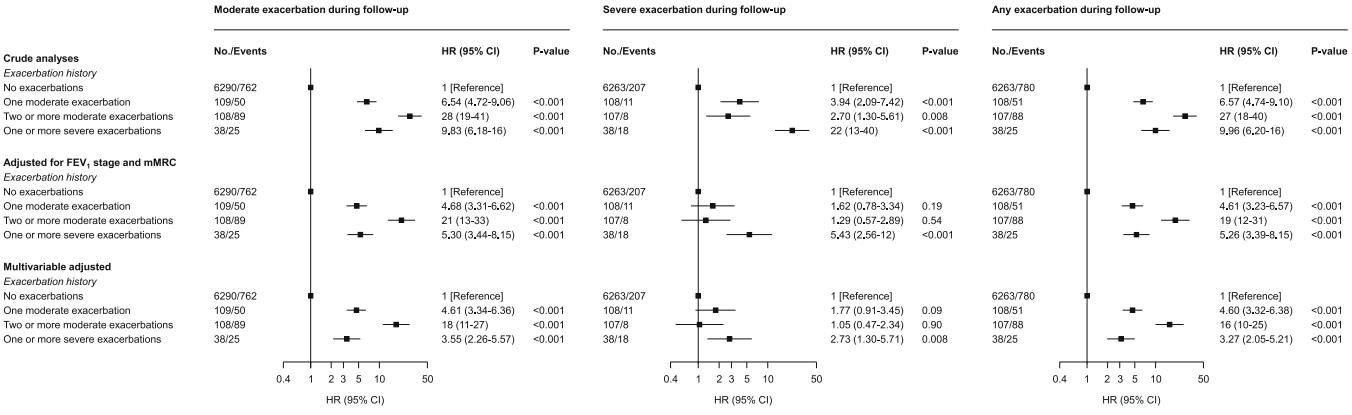

Fig. 3. Risk of moderate and severe exacerbations in individuals with COPD according to exacerbation history in the preceding year. Multivariable adjustment includes FEV_1 stage, modified Medical Research Council dyspnoea scale (mMRC), age, sex, civil status, smoking status, cumulative tobacco consumption, previous hospitalisation due to pneumonia and ischemic heart disease, and treatment. P-values obtained from Wald's test. COPD = chronic obstructive pulmonary disease.

from ECLIPSE, had only slightly higher exacerbation rates than those denoted as infrequent exacerbators (the two other groups). Although the most likely explanation for our finding is inclusion of mainly mild cases of COPD due to a general population setting, similar results were observed in other studies, which included more moderate and severe cases of COPD, including a Danish nationwide cohort study [25–28]. These results not only question whether exacerbation history can be used as a marker for the frequent exacerbator phenotype, as suggested in ECLIPSE [11], but also the very existence and stability of this particular phenotype. In addition, it seems that the GOLD classification system both over- and underestimates exacerbation risk in some subgroups [5,29,30], suggesting that the presently available disease markers still lack precision in predicting future exacerbations and that we need additional predictors.

A recent UK study identified individuals with COPD from an electronic general practice database and found that those with a severe exacerbation history had recurrent severe exacerbations, whereas those with a moderate exacerbation history, irrespective of frequency, had recurrent moderate exacerbations [27]. In accordance with our findings, these results also suggest the existence of different risk profiles according to type of exacerbation history and that even a single previous exacerbation predicts future exacerbation risk.

A limitation of the present study was the lack of post-bronchodilator spirometry to diagnose COPD. However, by defining airflow limitation in a high-risk population with the potential of developing COPD, we believe to have identified most COPD cases correctly. Nonetheless, a few cases with COPD (predominantly consisting of never-smokers and smokers with low tobacco consumption) were not included to enable a more precise case definition; however, as these cases would most likely be of mild degree, associations would only be diluted and could not account for the divergent results according to exacerbation history.

The clinical implication of the present study relates to identification

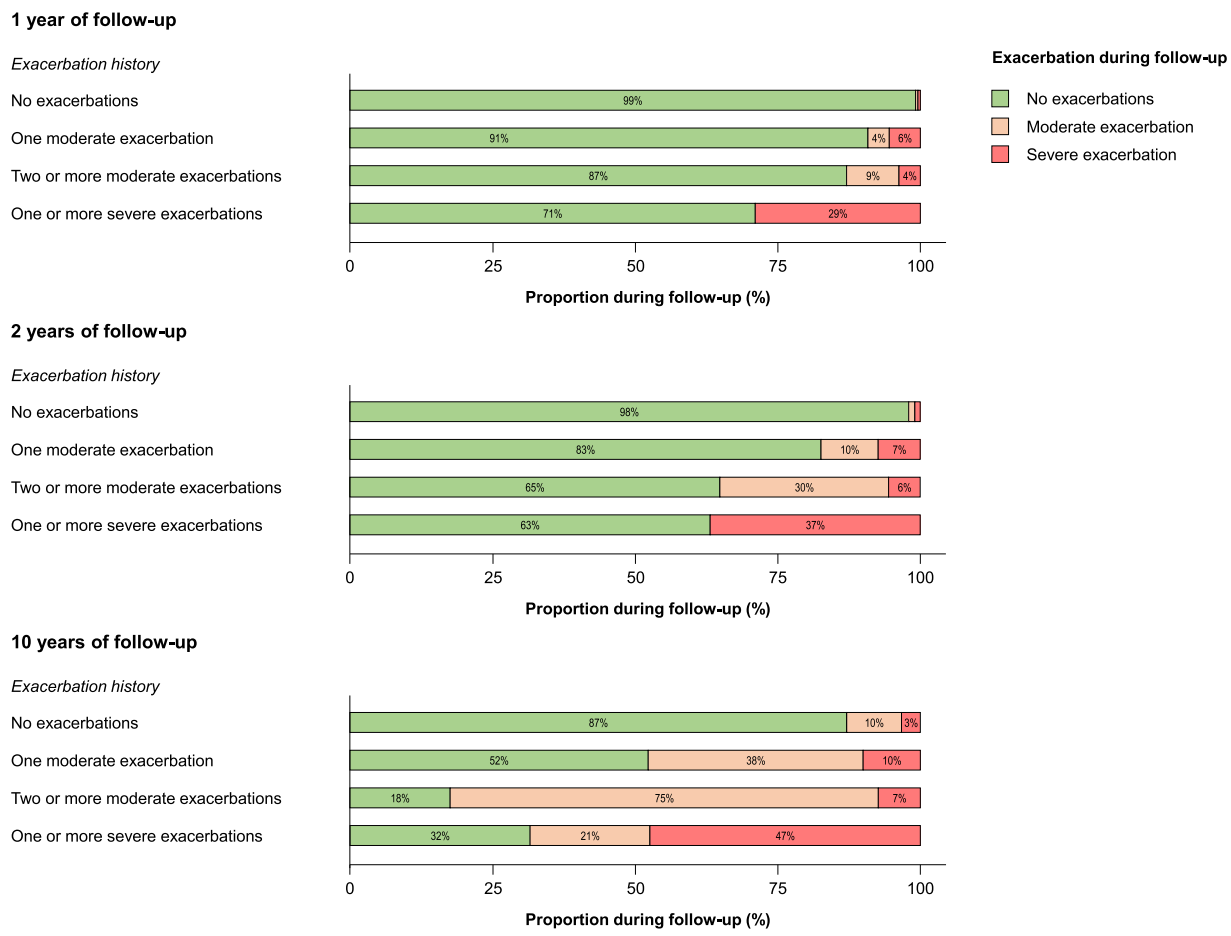

Fig. 4. Exacerbation profile after 1-, 2- and 10 years of follow-up in individuals with COPD according to exacerbation history in the preceding year. Numbers do not sum to 100% due to rounding. Numbers not specified when ≤1%. COPD = chronic obstructive pulmonary disease.

of high-risk patients for future exacerbations and preventive treatment. An exacerbation history irrespective of frequency and severity seems to be associated with increased risk of future exacerbation. Future studies should therefore investigate preventive treatment potential in individuals with only a single previous exacerbation. A history of severe exacerbation seems to identify the most vulnerable patients with the poorest prognosis and should therefore be a marker for need of additional interventions including palliative care, which has been widely underused among patients with COPD compared to patients with lung cancer [31].

In conclusion, individuals with COPD and a history of hospitalised exacerbations carried the poorest prognosis compared to those with a history of only medically treated exacerbations, suggesting difference in risk profile.

Author contributors

YÇ and PL had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses. YÇ, SA, JLM, BGN, JV, TSI, and PL contributed to the study concept and design. YÇ, SA, JLM, BGN, JV, TSI, and PL collected, analysed, or interpreted the data. YÇ wrote the draft manuscript and

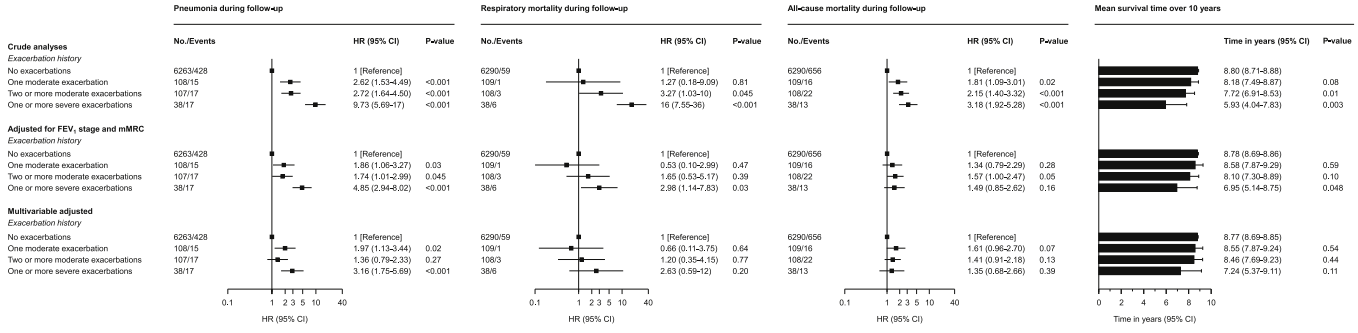

Fig. 5. Risk of pneumonia, respiratory mortality, and all-cause mortality in individuals with COPD according to exacerbation history in the preceding year. Multivariable adjustment includes FEV_1 stage, modified Medical Research Council dyspnoea scale (mMRC), age, sex, civil status, smoking status, cumulative tobacco consumption, previous hospitalisation due to pneumonia and ischemic heart disease, and treatment. P-values obtained from Wald's test. COPD = chronic obstructive pulmonary disease.

did the statistical analyses. YÇ, SA, JLM, BGN, JV, TSI, and PL revised the manuscript for important intellectual content. BGN obtained funding and provided administrative, technical, or material support. PL supervised the study.

Funding

The Lundbeck Foundation. The funder had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Conflicts of interest

YÇ reports personal fees from Boehringer Ingelheim and AstraZeneca outside the submitted work. JV reports personal fees from AstraZeneca, Boehringer-Ingelheim, Chiesi, GSK and Novartis and an institutional grant from Boehringer-Ingelheim. JV is supported by the NIHR Manchester Biomedical Research Centre. TS reports personal fees from AstraZeneca. PL reports grants from AstraZeneca and GlaxoSmithKline and personal fees from Boehringer Ingelheim, AstraZeneca, Novartis, and GlaxoSmithKline outside of the submitted work. SA, JLM, and BGN have nothing to disclose. The views expressed are those of the authors.

References

[1] Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2019 report. Global initiative for chronic obstructive lung disease, Available at: https://goldcopd.org/gold-reports/ (last accessed November 21, 2018).
[2] J.A. Wedzicha, T.A. Seemungal, COPD exacerbations: defining their cause and prevention, Lancet 370 (2007) 786–796.
[3] D.M. Halpin, M. Miravitlles, N. Metzdorf, B. Celli, Impact and prevention of severe exacerbations of COPD: a review of the evidence, Int. J. Chronic Obstr. Pulm. Dis. 12 (2017) 2891–2908.
[4] Y. Çolak, S. Afzal, B.G. Nordestgaard, J. Vestbo, P. Lange, Prognosis of asymptomatic and symptomatic, undiagnosed COPD in the general population in Denmark: a prospective cohort study, Lancet Respir Med 5 (2017) 426–434.
[5] P. Lange, J.L. Marott, J. Vestbo, et al., Prediction of the clinical course of chronic obstructive pulmonary disease, using the new GOLD classification: a study of the general population, Am. J. Respir. Crit. Care Med. 186 (2012) 975–981.
[6] A. Løkke, J.L. Marott, J. Mortensen, B.G. Nordestgaard, M. Dahl, P. Lange, New Danish reference values for spirometry, Clin. Res. J 7 (2013) 153–167.
[7] T.S. Ingebrigtsen, J.L. Marott, P. Lange, J. Hallas, B.G. Nordestgaard, J. Vestbo, Medically treated exacerbations in COPD by GOLD 1-4: a valid, robust, and seemingly low-biased definition, Respir. Med. 109 (2015) 1562–1568.
[8] J.P. Fine, R.J. Gray, A proportional hazards model for the subdistribution of a competing risk, J. Am. Stat. Assoc. 94 (1999) 496–509.
[9] P.K. Andersen, M.G. Hansen, J.P. Klein, Regression analysis of restricted mean survival time based on pseudo-observations, Lifetime Data Anal. 10 (2004) 335–350.
[10] J. Vestbo, S.S. Hurd, A.G. Agusti, et al., Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary, Am. J. Respir. Crit. Care Med. 187 (2013) 347–365.
[11] J.R. Hurst, J. Vestbo, A. Anzueto, et al., Susceptibility to exacerbation in chronic obstructive pulmonary disease, N. Engl. J. Med. 363 (2010) 1128–1138.
[12] G.C. Donaldson, T.A. Seemungal, A. Bhowmik, J.A. Wedzicha, Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease, Thorax 57 (2002) 847–852.
[13] M.T. Dransfield, K.M. Kunisaki, M.J. Strand, et al., Acute exacerbations and lung function loss in smokers with and without chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 195 (2017) 324–330.
[14] D.M. Halpin, M. Decramer, B. Celli, S. Kesten, D. Liu, D.P. Tashkin, Exacerbation frequency and course of COPD, Int. J. Chronic Obstr. Pulm. Dis. 7 (2012) 653–661.
[15] R.E. Kanner, N.R. Anthonisen, J.E. Connett, G. Lung Health Study Research, Lower respiratory illnesses promote FEV(1) decline in current smokers but not ex-smokers with mild chronic obstructive pulmonary disease: results from the lung health study, Am. J. Respir. Crit. Care Med. 164 (2001) 358–364.
[16] J. Vestbo, L.D. Edwards, P.D. Scanlon, et al., Changes in forced expiratory volume in 1 second over time in COPD, N. Engl. J. Med. 365 (2011) 1184–1192.
[17] J. Garcia-Aymerich, I. Serra Pons, D.M. Mannino, A.K. Maas, D.P. Miller, K.J. Davis, Lung function impairment, COPD hospitalisations and subsequent mortality, Thorax 66 (2011) 585–590.
[18] K.H. Groenewegen, A.M. Schols, E.F. Wouters, Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD, Chest 124 (2003) 459–467.
[19] R. McGhan, T. Radcliff, R. Fish, E.R. Sutherland, C. Welsh, B. Make, Predictors of rehospitalization and death after a severe exacerbation of COPD, Chest 132 (2007) 1748–1755.
[20] H. Mullerova, D.J. Maselli, N. Locantore, et al., Hospitalized exacerbations of COPD: risk factors and outcomes in the ECLIPSE cohort, Chest 147 (2015) 999–1007.
[21] J. Piquet, J.M. Chavaillon, P. David, et al., High-risk patients following hospitalisation for an acute exacerbation of COPD, Eur. Respir. J. 42 (2013) 946–955.
[22] J.J. Soler-Cataluna, M.A. Martinez-Garcia, P. Roman Sanchez, E. Salcedo, M. Navarro, R. Ochando, Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease, Thorax 60 (2005) 925–931.
[23] S. Suissa, S. Dell'Aniello, P. Ernst, Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality, Thorax 67 (2012) 957–963.
[24] G.C. Donaldson, H. Mullerova, N. Locantore, et al., Factors associated with change in exacerbation frequency in COPD, Respir. Res. 14 (2013) 79.
[25] M.K. Han, P.M. Quibrera, E.E. Carretta, et al., Frequency of exacerbations in patients with chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort, Lancet Respir Med 5 (2017) 619–626.
[26] M. Reilev, J. Lykkegaard, A. Halling, J. Vestbo, J. Sondergaard, A. Pottegard, Stability of the frequent COPD exacerbator in the general population: a Danish nationwide register-based study, NPJ Prim Care Respir Med 27 (2017) 25.
[27] K.J. Rothnie, H. Mullerova, L. Smeeth, J.K. Quint, Natural history of chronic obstructive pulmonary disease exacerbations in a general practice-based population with chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 198 (2018) 464–471.
[28] J.B. Soriano, M. Hahsler, C. Soriano, et al., Temporal transitions in COPD severity stages within the GOLD 2017 classification system, Respir. Med. 142 (2018) 81–85.
[29] A. Gedebjerg, S.K. Szepligeti, L.H. Wackerhausen, et al., Prediction of mortality in patients with chronic obstructive pulmonary disease with the new Global Initiative for Chronic Obstructive Lung Disease 2017 classification: a cohort study, Lancet Respir Med 6 (2018) 204–212.
[30] J.B. Soriano, B. Lamprecht, A.S. Ramirez, et al., Mortality prediction in chronic obstructive pulmonary disease comparing the GOLD 2007 and 2011 staging systems: a pooled analysis of individual patient data, Lancet Respir Med 3 (2015) 443–450.
[31] M.G. Husted, M. Kriegbaum, N. Kirkegaard, P. Lange, The use of healthcare resources in the last 3 years of life in patients with COPD and lung cancer in Denmark. A retrospective nationwide study, BMJ Support. Palliat. Care 4 (2014) 146–151.