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Predictors of re-exacerbation after an index exacerbation of chronic obstructive pulmonary disease in the REDUCE randomised clinical trial

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Summary

BACKGROUND: Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) compromise physical activity and quality of life and contribute significantly to health care costs. Systemic glucocorticoids benefit clinical outcome in AECOPD, and the REDUCE trial demonstrated noninferiority of a 5-day treatment course with prednisone compared with 14 days therapy regarding clinical outcome over 6 months of follow-up. Unexpectedly, we found an inverse correlation between circulating cortisol levels and exacerbation risk during a 6-month follow-up period.

OBJECTIVE: To evaluate whether additional predictors of COPD re-exacerbation can be identified after the index exacerbation in the REDUCE cohort.

METHODS: Of 314 patients with AECOPD randomised to 5 or 14 days of prednisone treatment, 311 were included in the analysis. Parameters tested as predictors of re-exacerbation were sex, age, smoking status, forced expiratory volume in one second (FEV_1), dyspnoea as assessed with the Medical Research Council (MRC) dyspnoea scale, home oxygen therapy, pretreatment with systemic glucocorticoids, pretreatment with antibiotics, duration of hospitalisation, blood pressure, oxygen saturation, admission to the Intensive Care Unit (ICU) and relevant infections in follow-up. The risks for re-exacerbation were estimated by means of logistic regression and Cox proportional hazard models and expressed as odds ratios and hazard ratios, respectively.

RESULTS: After multivariate adjustment, significant predictors at hospital discharge for COPD re-exacerbation during follow-up were: duration of hospital stay >8 days (hazard ratio [HR] 1.54, 95% confidence interval [CI] 1.03–2.28); FEV_1 <30% predicted (HR 1.76, 95% CI 1.06–2.91); hypertension (HR 2.39, 95% CI 1.04–5.48) and MRC dyspnoea scale (HR 1.61, 95% CI 1.30–2.01, per unit increment). Present cigarette smoking (HR 0.60, 95% CI 0.38–0.92) was negatively associated with re-exacerbation.

CONCLUSION: In addition to biochemical suppression of the adrenal glands, other standard clinical parameters predict re-exacerbation in patients admitted to the emergency department with AECOPD. (REDUCE trial registration: ISRCTN29646069)

Key words: *COPD; re-exacerbation; predictors*

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death worldwide [1]. Disease exacerbations have major implications for

COPD patients. They are usually associated with increased airway inflammation and characterised by a change in the patient's baseline dyspnoea, cough, and/or sputum purulence and volume [2–4] The main risk factor for the development of COPD is inhaled smoke. Additional risk factors include infections, continued oxidative damage and air pollution [5]. Patients' age, dyspnoea and airway obstruction are positive predictors for 2-year mortality [6]. Risk factors for exacerbations include older age, higher partial pressure of carbon dioxide ($PaCO_2$) and long-term use of systemic glucocorticoids [7], worse baseline breathlessness as measured with the Medical Research Council (MRC) dyspnoea scale [8–10], or poor nutritional status [11, 12]; in some patients no specific cause for an exacerbation can be found [5]. According to data from a Swiss cohort, approximately 20% of COPD patients experience at least one exacerbation per year [13, 14]. Affected patients require intensive monitoring and treatment, which contributes to high healthcare costs.

Exacerbations expedite the process of gradual decline in forced expiratory volume in 1 second (FEV_1) [15–17] and the progression of emphysema assessed with computed tomography (CT) [18]. Patients with frequent COPD exacerbations thus have worse health status, faster disease progression and a higher risk of hospital admission than patients with less frequent exacerbations [19].

Exacerbations become more frequent and severe with increasing COPD grade [4], but frequency of exacerbations varies widely among individuals [20], possibly because of varying susceptibility to viral infections [21]. To reduce exacerbation frequency is a main goal in COPD treatment.

One of the functional consequences of exacerbations is weakening of peripheral muscles, leading to decreased physical activity and quality of life [22]. Patients with an acute exacerbation in the previous year have a lower activity level than others without recent exacerbation [23]. Time spent outdoors declines during exacerbations, which indicates the importance of pulmonary rehabilitation after an exacerbation [24, 25]. Other factors such as depression may contribute to physical inactivity [26].

Baker and colleagues [27] reported that higher blood glucose concentrations in patients with acute exacerbations of COPD are associated with adverse clinical outcomes, including re-exacerbation. This finding may reflect the severity of the illness or the large dose of glucocorticoids used for exacerbation treatment.

The REDUCE randomised clinical trial [28] showed that a 5-day treatment with systemic glucocorticoids is noninferior to a 14-day treatment in patients admitted to the emergency department for acute exacerbations of COPD. In a prespecified prospective analysis of adrenal function, tested with the low-dose (1µg) corticotropin stimulation test, we found that basal and stimulated cortisol levels were inversely associated with the re-exacerbation risk, and a pathological result was associated with higher odds for re-exacerbation [29]. This novel finding was unexpected, indicating that existing knowledge of predictors may be limited. We therefore undertook the present study to identify possible additional predictors of re-exacerbation, using data from the REDUCE trial.

Patients and methods

Study design and patients

We used data from the REDUCE multicentre placebo-controlled trial [28, 30] (ISRCTN29646069) for the current analysis. The original trial was designed to test the hypothesis that in acute exacerbations of COPD, a 5-day treatment with systemic glucocorticoids would not be inferior to therapy for 14 days with regard to clinical outcome. Ethical approval to conduct the trial was obtained from the competent ethics committees (Ethikkommission beider Basel, currently named Ethikkommission Nordwest- und Zentralschweiz) and KEK Bern.

Briefly, patients admitted to the emergency department with exacerbated COPD were randomly assigned to 5 or 14 days of treatment with oral prednisone 40 mg daily. The primary outcome was the time to COPD re-exacerbation during the follow-up period of 6 months. Secondary endpoints included all-cause mortality, change in FEV_1, cumulative glucocorticoid dose and clinical performance (assessed with the MRC dyspnoea scale [9], a bronchitis-associated quality-of-life score [31], and patient-reported overall performance quantified on a visual analogue scale).

All data relevant to the primary and secondary endpoints were assessed daily during the hospitalisation period, on day 6, the day of discharge, and on days 15, 30, 90 and 180 of follow-up. Of the 314 randomised patients, 311 were considered in the statistical analyses; the remaining three were excluded because of an incorrect initial diagnosis [28].

Statistical analyses

For the current *post-hoc* analysis, data from the two treatment arms were pooled. We tested the following parameters as potential predictors for re-exacerbation: sex, age, smoking status, FEV_1, dyspnoea as assessed with the MRC dyspnoea scale, home oxygen therapy, pretreatment with systemic glucocorticoids, pretreatment with antibiotics, duration of hospitalisation, blood pressure, oxygen saturation, admission to the intensive care unit (ICU) and relevant infections in follow-up. Categorical variables are summarised as absolute and relative frequencies, and quantitative variables as mean and standard deviation or median and interquartile range, depending on their distributional properties. For group comparisons, the t-test or Wilcoxon rank-sum-test were used for quantitative variables and the chi^2-test or Fisher's exact test for qualitative variables. Correlations between two quantitative variables were quantified as Spearman's rank correlation coefficient. We used logistic regression models to investigate the associations of baseline factors with the risk for COPD re exacerbation, and re exacerbation and/or death, during follow-up. Models were adjusted for the following confounding variables: pretreatment with glucocorticoids, age, Global Initiative for Chronic Obstructive Lung Disease (GOLD) COPD grade, present smoking and sex. Survival methods were used to analyse time to re-exacerbation and time to re-exacerbation and/or death. In patients without an event during follow-up, the time to their last follow-up contact was considered as censored outcome. Kaplan-Meier plots and the log rank test were used to compare event times between groups. Associations of event times with predictor variables were assessed with Cox proportional hazard models, which were built in the same way as the logistic regression models. The proportional hazard assumption was tested on the basis of the Schoenfeld residuals [32]. To study the influence of time-varying predictor variables on the risk of an event, observation time was split into different periods defined by the date of discharge and the follow-up contacts, and predictor variables were updated at the start of each interval if they had been re-measured at this time point. For each of the variables measured repeatedly during follow-up, we assessed the relative importance of the most recent value and the value at discharge for predicting the risk of an event in the next time interval. For our statistical analyses we focused on the values of predictor variables at study inclusion (D0), day 6 (D6) and hospital discharge, since re-exacerbation events would occur after these time-points. The follow-up period was defined as the time between hospital discharge and study close-out after 6 months. A two-sided p-value of <0.05 was considered statistically significant. All calculations were done with Stata version 13.1 (StataCorp, College Station, TX, USA).

Results

Baseline characteristics of the study population are shown in table 1. An overview of quantitative variables at various study time-points is shown in supplementary table S1 (appendix).

A total of 113 out of the 311 analysed patients experienced one or more exacerbations during the follow-up of 180 days [28]. The proportion of patients experiencing a re-exacerbation was 40% with a COPD GOLD grade 4, 35% for grade 3, and 29% for grades 1 and 2.

Bivariate and multivariate analyses

For these analyses, we used FEV_1 in % predicted rather than the GOLD grade. Table 2 shows bivariate associations between possible predictor variables and the outcome variables "re-exacerbation" or "re-exacerbation and/or death". Previous smoking, a lower FEV_1, pretreatment with systemic glucocorticoids, use of home oxygen therapy, longer duration of hospitalisation and a higher score in the MRC dyspnoea scale were all associated with a higher hazard ratio for re-exacerbation or re-exacerbation and/or death at one or more time-points. Need for mechanical ventilation (defined as intubation or noninvasive ventilation) was not associated with the outcome variables at any time-point (not shown).

Table 1: Baseline characteristics of study participants. (Reproduced from ref. [29], with permission of the publisher.)

Characteristics	**Overall cohort (n = 311)**
Age (years), mean (SD)	69.8 (10.9)
Women, n (%)*	123 (39.5)
Smoking history	
Active smokers, n (%)	139 (45.1)
Pack years, median (quartiles)	50 (30, 60)
FEV_1 (% predicted), mean (SD)	31.5 (14.3)
GOLD COPD grade†, n (%)	
1	1 (0.3)
2	40 (13.3)
3	98 (32.6)
4	162 (53.8)
Medical Research Council dyspnoea scale‡, n (%)	
1	8 (2.7)
2	27 (9.3)
3	38 (13.0)
4	88 (30.5)
5	130 (44.5)
Home oxygen therapy, n (%)	40 (13.0)
Pretreatment with systemic glucocorticoids, n (%)§	63 (20.1)
Pretreatment daily prednisone dose (mg), median (quartiles)	20 (5, 50)
Pretreatment with antibiotics, n (%)¶	53 (17)
Clinical variables)	
Systolic blood pressure (mmHg), median (quartiles)	138 (124, 158)
Diastolic blood pressure (mmHg), median (quartiles)	80 (70, 90)
Heart rate (bpm), median (quartiles)	91 (80, 105)
Oxygen saturation with nasal oxygen (%), median (quartiles)	95 (92, 97)
Oxygen saturation without nasal oxygen (%), median (quartiles)	90 (86, 94)
Temperature (°C), median (quartiles)	37.3 (36.8, 38.1)

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in the first second; GOLD = Global Initiative for Chronic Obstructive Lung Disease; SD = standard deviation.
* p = 0.02
† Airflow limitation according to GOLD COPD grading: 1, mild; 2, moderate; 3, severe; 4, very severe
‡ Grading for severity of breathlessness according to the Medical Research Council questionnaire: 1, breathless only with strenuous exercise; 2, short of breath when hurrying on the level or up a slight hill; 3, walking slower than people of the same age on the level because of breathlessness, or stop for breath when walking at own pace on the level; 4, stop for breath after walking 100 yards or after a few minutes on the level; 5, too breathless to leave the house
§ Data refer to treatment prior to index acute COPD exacerbation, defined as daily therapy over 2 days or more directly before the day of inclusion.
¶ Data refer to treatment for the index acute COPD exacerbation.

Table 2: Bivariate analyses of potential predictor variables of time to re-exacerbation or re-exacerbation and/or death.

Predictor variable	Re-exacerbation Hazard ratio (95% CI)	p-value	Re-exacerbation and/or death Hazard ratio (95% CI)	p-value
Male	1		1	0.34
Female	0.91 (0.62–1.33)	0.63	0.84 (0.58–1.21)	
Age, years				
<65	1		1	
65–75	1.06 (0.66–1.72)	0.81	1.09 (0.68–1.75)	0.72
>75	1.30 (0.83–2.03)	0.25	1.42 (0.92–2.19)	0.11
Pack-years				
<40	1		1	
40–80	0.57 (0.38–0.86)	0.01	0.63 (0.42–0.94)	0.02
>80	0.93 (0.48–1.77)	0.81	0.90 (0.47–1.72)	0.76
FEV_1 (% predicted) D0				
≥50	1		1	
30–49	1.33 (0.71–2.48)	0.37	1.31 (0.72–2.40)	0.38
<30	1.54 (0.87–2.75)	0.14	1.57 (0.90–2.74)	0.11
FEV_1 (% predicted) D6				
≥50	1		1	
30–49	1.83 (1.14–2.94)	0.01	1.60 (1.01–2.52)	0.04
<30	2.25 (1.39–3.64)	0.00	2.21 (1.40–3.46)	0.00
FEV_1 (% predicted) discharge				
≥50	1		1	
30–49	1.58 (1.02–2.45)	0.04	1.45 (0.96–2.21)	0.08
<30	2.00 (1.26–3.17)	0.00	1.80 (1.16–2.81)	0.01
Pretreatment with systemic glucocorticoids				
Yes	1.61 (1.05–2.45)	0.03	1.65 (1.10–2.47)	0.02
No	1		1	
Active smokers				
Yes	0.56 (0.38–0.82)	0.00	0.56 (0.38–0.81)	0.00
No	1		1	
Home oxygen therapy				
Yes	2.27 (1.43–3.59)	0.00	2.51 (1.64–3.86)	0.00
No	1		1	
MRC dyspnoea scale D0				
1	1		1	
2	0.49 (0.12–2.07)	0.33	0.59 (0.15–2.37)	0.46
3	0.63 (0.17–2.32)	0.49	0.70 (0.19–2.54)	0.59
4	1.10 (0.34–3.59)	0.87	1.14 (0.35–3.69)	0.83
5	1.36 (0.42–4.34)	0.61	1.48 (0.46–4.71)	0.51

Table 2 (continued)				
MRC dyspnoea scale D6				
1	1		1	
2	1.28 (0.59–2.77)	0.53	1.45 (0.68–3.09)	0.34
3	1.97 (0.94–4.12)	0.07	2.09 (1.00–4.35)	0.05
4	1.66 (0.78–3.54)	0.19	1.79 (0.84–3.79)	0.13
5	1.89 (0.84–4.24)	0.12	2.00 (0.90–4.45)	0.09
MRC dyspnoea scale discharge				
1	1		1	
2	1.18 (0.54–2.56)	0.68	1.34 (0.63–2.87)	0.45
3	2.28 (1.08–4.83)	0.03	2.36 (1.12–4.99)	0.02
4	2.35 (1.08–5.12)	0.03	2.47 (1.14–5.33)	0.02
5	2.38 (0.88–6.38)	0.09	2.38 (0.89–6.39)	0.09
Length of hospitalisation				
>8 days	1.71 (1.16–2.51)	0.01	1.85 (1.27–2.69)	0.00
≤8 days	1		1	

CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in the first second; D0 = day of inclusion; D6 = day 6; MRC = Medical Research Council

Table 3 and table 4 show the results of the multivariate analyses for the outcomes re-exacerbation and re-exacerbation and/or death, respectively, with predictor variables assessed at inclusion, day 6 and discharge and adjusted for several potential confounder variables. The risk of re-exacerbation during follow-up was positively associated with a duration of hospital stay >8 days, low FEV_1, pretreatment with systemic glucocorticoids and use of home oxygen therapy. However, only the association with longer hospitalisation was statistically significant across all three time-points. Of the 139 active smokers, 39 (28.1%) had a re-exacerbation and 42 (30.2%) reached the endpoint re-exacerbation and/or death. Current smoking at the time of admission showed a significant negative association with the two outcomes. There was no evidence of an effect of sex, age or the need for mechanical ventilation on the two outcomes.

Table 3: Multivariate analyses of predictor variables of time to re-exacerbation.

	Time of measurement					
	D0		**D6**		**Discharge**	
	Hazard ratio (95% CI)	**p-value**	**Hazard ratio (95% CI)**	**p-value**	**Hazard ratio (95% CI)**	**p-value**
Male	1		1		1	
Female	0.94 (0.63–1.40)	0.75	0.94 (0.63–1.41)	0.78	0.97 (0.65–1.46)	0.90
Age, years						
<65	1		1		1	
65–75	0.87 (0.53–1.43)	0.58	0.85 (0.51–1.40)	0.51	0.80 (0.49–1.33)	0.40
>75	1.02 (0.63–1.66)	0.94	1.00 (0.61–1.62)	0.99	0.99 (0.61–1.60)	0.97
Group*						
Conventional treatment	1		1		1	
Short-term treatment	0.94 (0.64–1.38)	0.75	0.97 (0.66–1.42)	0.88	0.92 (0.63–1.35)	0.67

Table 3 (continued)						
Home oxygen therapy						
Yes	1.46 (0.86–2.47)	0.16	1.27 (0.74–2.18)	0.38	1.29 (0.75–2.22)	0.35
No	1		1		1	
Active smoker						
Yes	0.62 (0.40–0.96)	0.03	0.58 (0.37–0.90)	0.02	0.60 (0.38–0.92)	0.02
No	1		1		1	
Pretreatment with systemic glucocorticoids						
Yes	1.44 (0.90–2.30)	0.13	1.52 (0.95–2.43)	0.08	1.40 (0.87–2.24)	0.16
No	1		1		1	
Length of hospitalisation						
>8 days	1.54 (1.03–2.28)	0.03	1.44 (0.97–2.15)	0.07	1.54 (1.03–2.28)	0.03
≤8 days	1		1		1	
FEV_1 (% predicted)						
≥50	1		1		1	
30–49	1.33 (0.71–2.50)	0.37	1.89 (1.16–3.08)	0.01	1.46 (0.94–2.27)	0.10
<30	1.44 (0.79–2.62)	0.24	1.86 (1.12–3.08)	0.02	1.76 (1.06–2.91)	0.03

CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in the first second; D0 = day of inclusion; D6 = day 6
All variables listed in the table were simultaneously included in the model.
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Table 4: Multivariate analyses of predictor variables of time to re-exacerbation and/or death.

	Time of measurement					
	D0		**D6**		**Discharge**	
	Hazard ratio (95% CI)	**p-value**	**Hazard ratio (95% CI)**	**p-value**	**Hazard ratio (95% CI)**	**p-value**
Male	1		1		1	
Female	0.84 (0.57–1.24)	0.38	0.84 (0.57–1.25)	0.39	0.86 (0.58–1.28)	0.46
Age, years						
<65	1		1		1	
65–75	0.90 (0.55–1.47)	0.68	0.89 (0.54–1.45)	0.63	0.85 (0.52–1.38)	0.51
>75	1.12 (0.70–1.79)	0.64	1.10 (0.69–1.76)	0.68	1.08 (0.68–1.72)	0.75
Group*						
Conventional treatment	1		1		1	
Short-term treatment	0.87 (0.60–1.26)	0.47	0.90 (0.62–1.30)	0.56	0.86 (0.60–1.25)	0.43

Table 4 (continued)

Home oxygen therapy						
Yes	1.53 (0.97–2.61)	0.07	1.41 (0.85–2.35)	0.18	1.49 (0.89–2.48)	0.13
No	1		1		1	
Active smoker						
Yes	0.67 (0.44–1.02)	0.06	0.64 (0.42–0.98)	0.04	0.65 (0.43–0.99)	0.046
No	1		1		1	
Pretreatment with systemic glucocorticoids						
Yes	1.48 (0.95–2.32)	0.09	1.54 (1.06–2.30)	0.03	1.46 (0.93–0.28)	0.10
No	1		1		1	
Length of hospitalisation						
>8 days	1.65 (1.12–2.42)	0.01	1.56 (1.08–2.30)	0.03	1.65 (1.12–2.43)	1.01
≤8 days	1		1		1	
FEV_1 (% predicted)						
≥50	1		1		1	
30–49	1.30 (0.70–2.39)	0.40	1.59 (1.00–2.55)	0.05	1.29 (0.84–1.97)	0.24
<30	1.43 (0.80–2.56)	0.22	1.73 (1.07–2.80)	0.03	1.49 (0.91–2.42)	0.11

CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in the first second; D0 = day of inclusion; D6 = day 6
All variables listed in the table were simultaneously included in the model.
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Stratified analyses

Analyses were stratified by age (<65 years, 65–75 years, >75 years), sex and FEV1% predicted at discharge (≥50%, 30–49%, <30%). However, there was no evidence that these factors modified the effects of other predictor variables (see appendix, tables S2A to S4B).

Survival analyses

We calculated the hazard ratios of re-exacerbation or re-exacerbation and/or death associated with various predictor variables at baseline. As depicted in figure 1, panels A–D, smoking status, MRC dyspnoea scale score and duration of hospital stay were all statistically significant predictors of re-exacerbation. This was also the case for re-exacerbation and/or death (data not shown). Associations of the two risks with the predictor variable hypertension were also positive but not statistically significant. The association of re-exacerbation with FEV_1 was analysed at baseline, day 6 and hospital discharge (fig. 2). It was negative across all three time-points and reached statistical significance at D6 (panel B) and discharge (panel C). Again, results were similar for the outcome re-exacerbation and/or death.

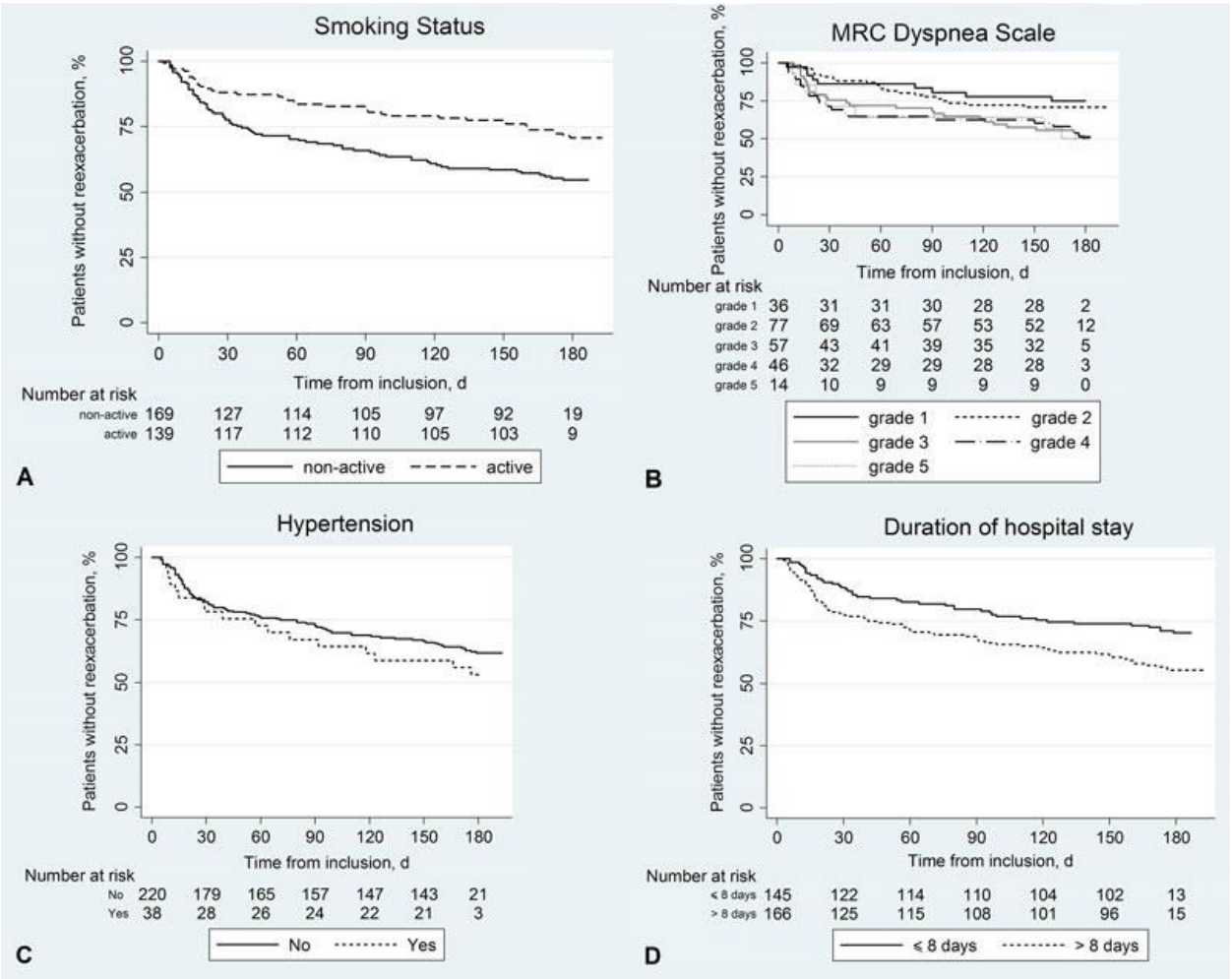

Figure 1: Survival curves according to various predictor variables at discharge.

The curves show the proportions of patients without re-exacerbation during follow-up over time: (A) active smoking (yes vs no, p(log rank test) = 0.003), (B) Medical Research Council dyspnoea scale (levels 1 to 5, p = 0.02), (C) hypertension (yes vs no, p = 0.30) and (D) duration of hospital stay (>8 vs ≤8 days, p = 0.006).

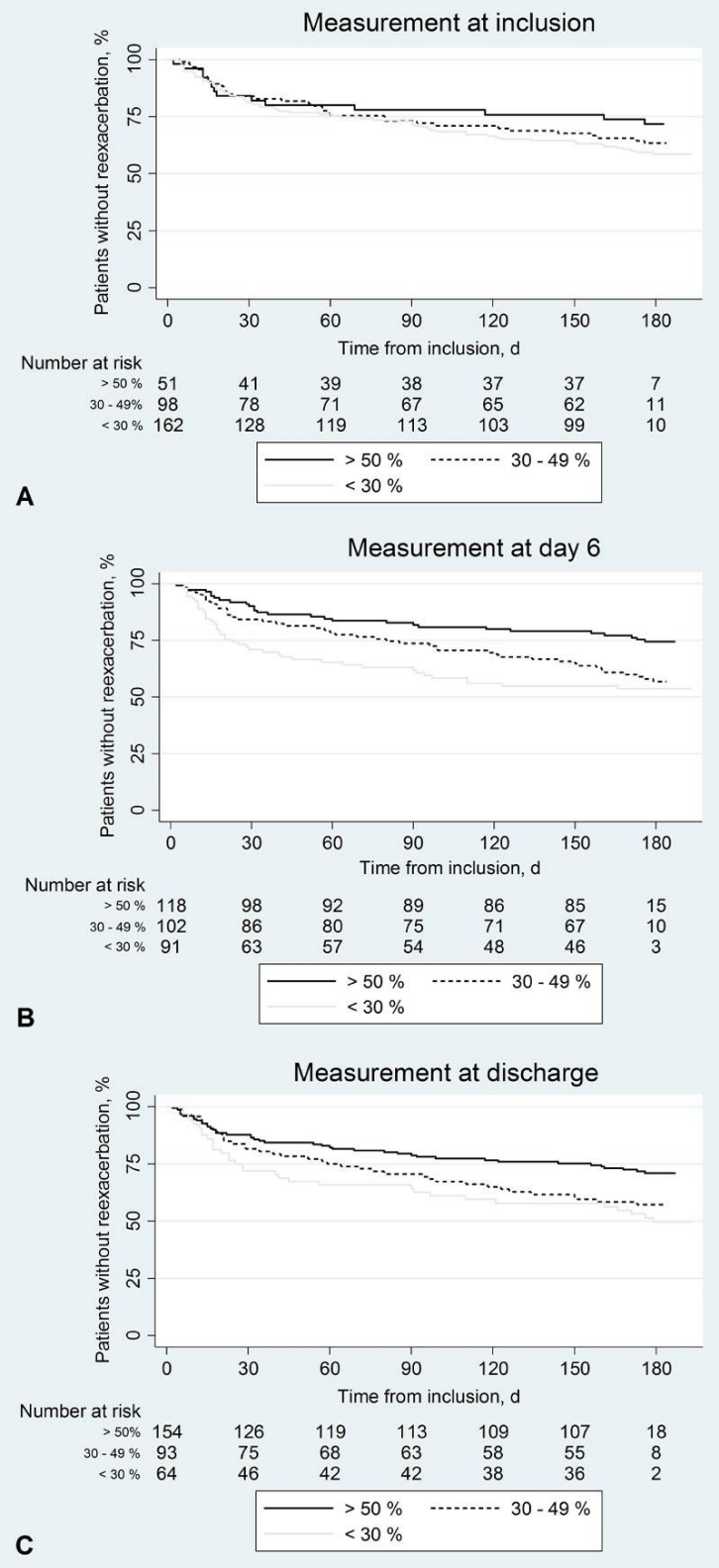

Figure 2: Survival curves according to forced expiratory volume in 1 second (FEV_1) at baseline, day 6 and discharge.

Proportions of patients without re-exacerbation during follow-up for different categories of FEV_1 in % predicted (<30%, 30–50%, >50%): (A) at inclusion (p(log rank test) = 0.31), (B) at day 6 (p = 0.003) and (C) at discharge (p = 0.008).

Time-varying predictor variables

Results of the analyses for the outcome re-exacerbation are shown in table 5. Using Cox-proportional hazards models with different consecutive time periods to take into account changes in predictor variables during follow-up, we found that smoking during follow up showed a significant negative association with the risk of re-exacerbation in the next time period (HR 0.47, p = 0.04), whereas smoking at discharge showed a positive but not statistically significant association. The measurements of lung function, hypertension and the MRC dyspnoea score during follow-up also showed stronger associations with the subsequent risk of re-exacerbation than the corresponding values measured at discharge. A high MRC dyspnoea score at follow-up was strongly predictive of a re-exacerbation in the next time period.

Table 6 shows the results of the corresponding analyses for the outcome re-exacerbation and/or death. Hazard ratios were comparable to the ones for re-exacerbation in table 5.

Table 5: Hazard ratios of re-exacerbation associated with the p-values of predictor variables at discharge and during follow-up.

Predictor variable	Measurement at discharge Hazard ratio (95% CI)	p-value	Measurement during follow-up* Hazard ratio (95% CI)	p-value
FEV_1, % predicted	1.00 (0.97–1.02)	0.86	0.98 (0.95–1.00)	0.06
FVC, % predicted	1.00 (0.99–1.02)	0.83	0.99 (0.98–1.00)	0.20
Weight, kg	1.04 (0.92–1.17)	0.54	0.96 (0.86–1.08)	0.55
Hyperglycaemia	1.13 (0.71–1.79)	0.61	1.36 (0.76–2.42)	0.30
Hypertension	1.10 (0.56–2.19)	0.78	2.39 (1.04–5.48)	0.04
ICU	1.38 (0.61–3.11)	0.44	1.36 (0.75–2.48)	0.32
Pulse	1.07 (0.90–1.28)	0.43	1.03 (0.87–1.22)	0.73
Systolic blood pressure	1.06 (0.94–1.20)	0.32	0.98 (0.87–1.09)	0.68
Diastolic blood pressure	0.85 (0.68–1.07)	0.17	1.08 (0.89–1.31)	0.46
MRC dyspnoea scale	1.01 (0.82–1.26)	0.90	1.61 (1.30–2.01)	0.00
Health score – doctor	0.94 (0.81–1.08)	0.38	0.92 (0.83–1.02)	0.11
Health score – patient	0.90 (0.80–1.03)	0.13	0.95 (0.84–1.08)	0.42
Infection	0.95 (0.30–3.02)	0.93	0.93 (0.56–1.56)	0.80
Oxygen saturation without administered O_2	1.08 (0.42–2.76)	0.88	0.68 (0.31–1.50)	0.34

CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in the first second; FVC = forced vital capacity; ICU = intensive care unit admission; MRC = Medical Research Council

Observation time was split into periods defined by the date of discharge and the follow-up contacts, and predictor variables were updated at the start of each interval if they had been re-measured at this time point. For each of the variables, the most recent value and the value at discharge were simultaneously included as predictors of re-exacerbation in the next time period.

* Including the time-points day 6, discharge, and days 15, 30, 90 and 180

Table 6: Hazard ratios of re-exacerbation and/or death associated with the p-values of predictor variables at discharge and during follow-up.

Predictor variable	Measurement at discharge Hazard ratio (95% CI)	p-value	Measurement during follow-up* Hazard ratio (95% CI)	p-value
FEV_1, % predicted	1.00 (0.98–1.03)	0.80	0.98 (0.95–1.00)	0.03
FVC, % predicted	1.00 (0.99–1.02)	0.73	0.99 (0.98–1.00)	0.18
Weight	1.04 (0.93–1.16)	0.52	0.97 (0.86–1.08)	0.55
Hyperglycaemia	1.06 (0.67–1.67)	0.80	1.46 (0.84–2.55)	0.18
Hypertension	1.13 (0.58–2.19)	0.73	2.57 (1.15–5.73)	0.02
ICU	1.41 (0.63–3.14)	0.41	1.32 (0.72–2.40)	0.37
Pulse	1.06 (0.89–1.26)	0.51	1.02 (0.87–1.21)	0.77
Systolic blood pressure	1.07 (0.95–1.20)	0.28	0.96 (0.86–1.08)	0.50
Diastolic blood pressure	0.85 (0.68–1.06)	0.14	1.07 (0.88–1.29)	0.51
MRC dyspnoea scale	1.00 (0.81–1.23)	0.98	1.62 (1.31–2.00)	0.00
Health score – doctor	0.89 (0.78–1.02)	0.10	0.96 (0.86–1.06)	0.38
Health score – patient	0.91 (0.80–1.03)	0.13	0.97 (0.86–1.09)	0.60
Infection	0.99 (0.31–3.16)	0.99	0.91 (0.55–1.50)	0.71
Oxygen saturation without administered O_2	1.07 (0.43–2.64)	0.89	0.69 (0.32–1.48)	0.34

CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in the first second; FVC = forced vital capacity; ICU = intensive care unit admission; MRC = Medical Research Council

Observation time was split into periods defined by the date of discharge and the follow-up contacts, and predictor variables were updated at the start of each interval if they had been re-measured at this time point. For each of the variables, the most recent value and the value at discharge were simultaneously included as predictors of re-exacerbation in the next time period.

* Including the time-points day 6, discharge, and days 15, 30, 90 and 180

Discussion

Prompted by our observation that low serum cortisol levels were inversely associated with COPD re-exacerbation risk [29], we used prospectively gathered data from the "REDUCE" trial [28] to identify additional predictors of re-exacerbation. Our data show that lower FEV_1, a history of past (but not active) smoking, hospitalisation >8 days, hypertension and a higher score on the MRC dyspnoea scale all significantly predict COPD re-exacerbation. In contrast, a recent Norwegian study about predictors of exacerbations showed that female sex, higher age, a history of exacerbations the year before inclusion, higher GOLD grade, chronic cough and use of inhaled corticosteroids were significant predictors of an increased risk of exacerbations [33].

We consider discharge from the hospital as the most reliable time-point for our analyses since patients should have regained their former steady-state level of lung function and general health at this time.

Our observation that low FEV_1 predicts an increased re-exacerbation risk is consistent with previous studies showing an association between exacerbation frequency and decreasing lung function in COPD [15–17, 19], and between low FEV_1 and readmission risk [34, 35]. FEV_1 impairment is acknowledged as one of the major prognostic factors in the COPD GOLD report [2].

Surprisingly, current smoking at hospital admission, on day 6 at discharge and at later time-points was associated with a significantly lower risk of re-exacerbation than past smoking status. Current smoking has also been found to be negatively associated with hospitalisation for COPD exacerbation in a previous case-control study [36]. Our finding may be explained by a selection bias referred to as the "healthy smoker effect" [37], observed before in patients with asthma. Asthma patients with pronounced respiratory symptoms (e.g., coughing) seem to be more likely to quit smoking earlier than those who are relatively resistant to its unpleasant effects [38]. There is also evidence that sympto-

matic COPD patients are more likely to stop smoking [39]. This selective process is likely to bias the relationship between smoking and COPD re-exacerbation, disguising the causal effect of smoking [38, 40].

Interestingly, we identified new or worsening hypertension during follow-up as a significant predictor of COPD re-exacerbation. The Swiss COPD cohort similarly found that, cardiovascular diseases were associated with future exacerbation (in addition to previous rehabilitation, hospitalisation and a history of exacerbation) [41]. Arterial hypertension and COPD are often present in the same individual [42–44], and it has been speculated that low-grade systemic inflammation may be a common pathogenic factor in both medical conditions [45].

In the survival analyses, hospital stay >8 days and a higher grade of breathlessness as assessed by the MRC dyspnoea scale were significantly associated with the re-exacerbation risk. These observations are consistent with previous studies of the MRC dyspnoea scale, COPD exacerbations and length of hospital stay [10, 46, 47].

Our study has several limitations. The REDUCE trial was not designed specifically to identify risk factors of COPD re-exacerbation. Therefore, the causal relation between the predictors and outcome remains unproven. Additional limiting factors include the relatively small sample size, and the follow-up period of merely 6 months, during which time only approximately 36% of the study participants experienced a re-exacerbation [28]. Also, the trial was performed in only one country, precluding generalisation of our findings to populations outside Switzerland.

In conclusion, our study identified very severe COPD stage, hypertension, dyspnoea severity, and COPD-associated hospitalisation >8 days to be associated with an increased risk of COPD re-exacerbation. The identification of affected patients might facilitate preventive steps, such as extended planning of patient care after hospital discharge [48]. Our findings hold implications for future studies on tools to evaluate the risk of COPD re-exacerbation.

Disclosure statement
No financial support and no other potential conflict of interest relevant to this article was reported.

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Appendix: Supplementary tables

Note:

Medical Research Council (MRC) dyspnoea scale (adapted from: Fletcher, C.M. The clinical diagnosis of pulmonary emphysema; an experimental study. Proceedings of the Royal Society of Medicine 1952;45:577–584):

1: no breathlessness except for strong exercises;

2: short of breath when walking up a hill or stairs;

3: unable to keep up with contemporaries because of breathlessness, able to walk a mile or more at his own speed;

4: stops for breath after walking about 100 yards;

5: too breathless on talking or breathless on dressing or undressing.

Abbreviations used in supplementary tables:

CI = confidence interval

D0 = day of inclusion

D6 = day 6

D30 = day 30

D90 = day 90

D180 = day 180

FEV_1 = forced expiratory volume in first second

FEV_1 % pred. = FEV_1 % predicted

FVC = forced vital capacity

HR = hazard ratio

OR = odds ratio

SaO_2 = oxygen saturation

Table S1: Characteristics of quantitative variables.

Variable	Time point	Mean	Std. Dev	Min	Max	P25	P50	P75
Age (years) n = 311		69.8	10.9	42.8	97.7	61.6	70.9	78.1
Pack-years smoked n = 293		50	23.7	10	150	30	50	60
Duration of hospitalisation (d) n = 311		10.2	6.7	1	38	6	9	13
Temperature (°C) n = 296		37.5	0.9	36	39.9	36.8	37.3	38.1
Time to exacerbation (d) n = 309		129.1	69.7	2	193	57	179	179
Time to death (d) n = 309		172.2	45.5	2	475	179	179	179
Cumulative dose steroids (mg) n = 309		594.2	516.3	200	3324	200	560	600
FEV_1 (% predicted) n = 305	D0	31.5	14.3	7.1	81	21	28	41
FEV_1 (L) n = 301	D0	0.8	0.4	0.25	2.18	0.5	0.68	0.97
Tiffeneau (FEV_1/FVC) n = 300	D0	0.46	0.12	0.15	0.82	0.36	0.45	0.55

Table S1 (continued)								
Heart rate (bpm) n = 304	D0	93.4	18.9	47	159	80	91	105
Systolic blood pressure (mm Hg) n = 307	D0	141.4	25.6	87	220	124	138	158
Diastolic blood pressure (mm Hg) n = 307	D0	80.5	15.1	44	130	70	80	90
SaO_2 with administered O_2 (%) n = 247	D0	94.1	3.5	84	100	92	95	97
SaO_2 without administered O_2 (%) n = 210	D0	88.4	7.5	54	100	86	90	94
FEV_1 (% predicted) n = 289	D6	42.1	18.4	12	102	28	39	55
FEV_1 (L) n = 289	D6	1.03	0.5	0.32	2.83	0.67	0.93	1.3
Tiffeneau (FEV_1/FVC) n = 288	D6	0.48	0.14	0.16	0.94	0.38	0.46	0.58
Systolic blood pressure (mm Hg) n = 294	D6	133.5	20.5	80	205	120	131.5	149
Diastolic blood pressure (mm Hg) n = 294	D6	75	11.4	40	108	70	75	80
SaO_2 with administered O_2 (%) n = 89	D6	92.1	10.2	0	99	91	93	95
SaO_2 without administered O_2 (%) n = 193	D6	92.1	4.8	60	99	90	93	95
Weight (kg) n = 293	D6	72.6	18.3	35	134	60	72	83
FEV_1 (% predicted) n = 237	Discharge	43.5	17.6	12	101	29	43	55
FEV_1 (L) n = 237	Discharge	1.05	0.5	0.32	2.83	0.71	1	1.3
Tiffeneau (FEV_1/FVC) n = 237	Discharge	0.49	0.14	0.16	0.95	0.39	0.47	0.58

Table S1 (continued)								
Systolic blood pressure (mm Hg) n = 251	Discharge	128.8	19.7	90	185	115	130	140
Diastolic blood pressure (mm Hg) n = 251	Discharge	72.8	10	40	100	68	73	80
SaO_2 with administered O_2 (%) n = 42	Discharge	93.3	3.2	84	98	92	93.5	96
SaO_2 without administered O_2 (%) n = 161	Discharge	92.1	7.6	8	99	90	93	96
Weight (kg) n = 248	Discharge	72	19	36	132	58	72	84
FEV_1 (% predicted) n = 245	D30	47.4	20	10	110	32	44	62
FEV_1 (L) n = 245	D30	1.19	0.6	0.25	3.32	0.79	1.03	1.57
Tiffeneau (FEV_1/FVC) n = 245	D30	0.50	0.14	0.19	0.91	0.40	0.50	0.61
Systolic blood pressure (mm Hg) n = 246	D30	130.3	20.5	73	201	119	130	142
Diastolic blood pressure (mm Hg) n = 245	D30	75.7	12.5	25	110	69	75	84
SaO_2 with administered O_2 (%) n = 25	D30	92	4	81	98	89	93	94
SaO_2 without administered O_2 (%) n = 161	D30	92.7	8.4	0	100	92	94	96
FEV_1 (% predicted) n = 205	D180	46.8	19.5	8	105	31	42	60
FEV_1 (L) n = 205	D180	1.18	0.6	0.31	3.26	0.79	1.02	1.48
Tiffeneau (FEV_1/FVC) n = 203	D180	0.49	0.14	0.16	0.94	0.39	0.49	0.59
Heart rate (bpm) n = 203	D180	78.6	13.8	51	122	69	77	86

Table S1 (continued)								
Systolic blood pressure (mm Hg) n = 210	D180	133.1	20.6	84	199	120	131	142
Diastolic blood pressure (mm Hg) n = 210	D180	77	11.6	43	106	70	77.5	85
SaO_2 with administered O_2 (%) n = 14	D180	86.8	25.1	0	98	91	93.5	95
SaO_2 without administered O_2 (%) n = 132	D180	93.7	3.1	84	100	92	94	96
Weight (kg) n = 218	D180	73.2	18.9	35	134	60	72	85

Table S2A: Multivariate analysis of time to re-exacerbation or re-exacerbation and/or death stratified by age at discharge.

	<65 years HR (95%CI)	**65–75 years HR (95%CI)**	**>75 years HR (95%CI)**	**Heterogeneity p-value***
Re-exacerbation				
Women *p-value*	0.56 (0.24–1.31) *0.18*	1.10 (0.50–2.38) *0.82*	1.37 (0.74–2.53) *0.32*	0.24
Short-term group *p-value*	0.90 (0.42–1.93) *0.78*	0.76 (0.37–1.58) *0.46*	0.91 (0.51–1.63) *0.76*	0.92
Home oxygen therapy *p-value*	1.27 (0.34–4.77) *0.72*	2.43 (0.83–7.14) *0.11*	0.86 (0.39–1.88) *0.70*	0.31
Active smokers *p-value*	0.63 (0.29–1.38) *0.25*	1.03 (0.49–2.15) *0.94*	0.26 (0.10–0.64) *0.00*	0.07
Pretreatment with systemic glucocorticoids *p-value*	2.15 (0.76–6.05) *0.15*	0.58 (0.21–1.61) *0.30*	2.05 (1.01–4.13) *0.046*	0.10
Hospitalisation >8 days *p-value*	1.18 (0.58–2.40) *0.65*	1.36 (0.67–2.77) *0.39*	2.06 (1.06–4.03) *0.03*	0.50
FEV_1 (% predicted) discharge *p-value*	1.19 (0.77–1.84) *0.42*	1.49 (0.90–2.47) *0.12*	1.43 (0.94–2.20) *0.10*	0.76

Table S2A (continued)				
Re-exacerbation and/or death				
Women *p-value*	0.49 (0.21–1.16) *0.10*	0.95 (0.44–2.04) *0.90*	1.16 (0.64–2.09) *0.63*	0.27
Short-term group *p-value*	0.77 (0.36) *0.49*	0.69 (0.34–1.41) *0.31*	0.92 (0.53–1.59) *0.77*	0.81
Home oxygen therapy *p-value*	1.64 (0.46–5.87) *0.45*	2.38 (0.82–6.94) *0.11*	1.12 (0.54–2.31) *0.77*	0.51
Active smokers *p-value*	0.75 (0.34–1.64) *0.47*	0.98 (0.47–2.02) *0.95*	0.35 (0.16–0.78) *0.01*	0.16
Pretreatment with systemic glucocorticoids *p-value*	2.31 (0.82–6.45) *0.11*	0.58 (0.21–1.59) *0.29*	2.11 (1.10–4.06) *0.03*	0.08
Hospitalisation >8 days *p-value*	1.07 (0.53–2.16) *0.85*	1.51 (0.75–3.04) *0.24*	2.35 (1.22–4.54) *0.01*	0.27
FEV_1 (% predicted) discharge *p-value*	1.11 (0.72–1.71) *0.64*	1.42 (0.87–2.31) *0.16*	1.24 (0.82–1.87) *0.30*	0.76
All variables listed in the table were simultaneously included in the model. * Chi^2-Test				

Table S2B: Multivariate analysis of re-exacerbation or re-exacerbation and/or death stratified by age at discharge.

	<65 years OR (95% CI)	**65–75 years OR (95% CI)**	**>75 years OR (95% CI)**	**Heterogeneity p-value***
Re-exacerbation				
Women *p-value*	0.55 (0.21–1.43) *0.22*	1.30 (0.48–3.49) *0.61*	1.65 (0.67–4.03) *0.28*	0.23
Short-term group *p-value*	1.11 (0.44–2.83) *0.82*	0.86 (0.34–2.15) *0.74*	0.84 (0.37–1.95) *0.69*	0.90
Home oxygen therapy *p-value*	1.01 (0.17–6.12) *1.00*	3.24 (0.70–14.9) *0.13*	0.92 (0.29–2.90) *0.89*	0.41
Active smokers *p-value*	0.50 (0.18–1.37) *0.18*	0.98 (0.38–2.53) *0.96*	0.19 (0.06–0.61) *0.01*	0.10
Pretreatment with systemic glucocorticoids *p-value*	2.41 (0.68–8.54) *0.17*	0.45 (0.13–1.59) *0.21*	1.74 (0.58–5.17) *0.32*	0.14
Hospitalisation >8 days *p-value*	1.27 (0.50–3.25) *0.61*	1.40 (0.56–3.51) *0.47*	2.85 (1.17–6.94) *0.02*	0.40
FEV1 (% predicted) discharge *p-value*	1.26 (0.70–2.24) *0.44*	1.86 (1.00–3.47) *0.05*	1.93 (1.07–3.48) *0.03*	0.53

Table S2B (continued)				
Re-exacerbation and/or death				
Women *p-value*	0.46 (0.17–1.23) *0.12*	1.04 (0.39–2.77) *0.94*	1.12 (0.46–2.72) *0.80*	0.38
Short-term group *p-value*	0.94 (0.37–2.39) *0.89*	0.72 (0.29–1.79) *0.48*	0.74 (0.32–1.73) *0.49*	0.91
Home oxygen therapy *p-value*	1.84 (0.29–11.6) *0.51*	2.94 (0.64–13.5) *0.17*	1.81 (0.54–6.03) *0.34*	0.88
Active smokers *p-value*	0.62 (0.23–1.71) *0.36*	0.86 (0.33–2.23) *0.76*	0.28 (0.10–0.80) *0.02*	0.28
Pretreatment with systemic glucocorticoids *p-value*	2.61 (0.74–9.18) *0.14*	0.44 (0.12–1.54) *0.20*	2.14 (0.69–6.67) *0.19*	0.09
Hospitalisation >8 days *p-value*	1.09 (0.43–2.81) *0.85*	1.72 (0.69–4.29) *0.24*	3.90 (1.60–9.50) *0.00*	0.15
FEV1 (% predicted) discharge *p-value*	1.15 (0.64–2.07) *0.65*	1.74 (0.94–3.22) *0.08*	1.63 (0.90–2.96) *0.11*	0.58
All variables listed in the table were simultaneously included in the model. * Chi^2-Test				

Table S3A: Multivariate analysis of time to re-exacerbation or re-exacerbation and/or death stratified by FEV_1 at discharge.				
	FEV_1 (% pred.) ≥50% HR (95%CI)	**FEV_1 (% pred.) 30–49% HR (95%CI)**	**FEV_1 (% pred.) <30% HR (95%CI)**	**Heterogeneity p-value***
Re-exacerbation				
Women *p-value*	1.39 (0.72–2.68) *0.33*	0.65 (0.30–1.39) *0.27*	1.10 (0.51–2.37) *0.80*	0.33
Age *p-value*	0.96 (0.66–1.41) *0.85*	1.19 (0.70–2.03) *0.52*	0.94 (0.58–1.52) *0.79*	0.77
Short-term group *p-value*	1.17 (0.60–2.27) *0.64*	0.92 (0.47–1.79) *0.80*	0.60 (0.27–1.33) *0.21*	0.45
Home oxygen therapy *p-value*	2.50 (0.81–7.72) *0.11*	1.19 (0.48–2.95) *0.71*	0.97 (0.41–2.32) *0.95*	0.41
Active smokers *p-value*	0.54 (0.26–1.12) *0.10*	0.70 (0.29–1.68) *0.42*	0.61 (0.27–1.38) *0.24*	0.91
Pretreatment with systemic glucocorticoids *p-value*	1.00 (0.41–2.47) *1.00*	1.42 (0.58–3.48) *0.45*	2.03 (0.90–4.57) *0.09*	0.52

Table S3A (continued)				
Hospitalisation >8 days *p-value*	1.32 (0.67–2.59) *0.43*	1.57 (0.76–3.27) *0.22*	1.56 (0.75–3.24) *0.23*	0.92
Re-exacerbation and/or death				
Women *p-value*	1.08 (0.58–2.02) *0.82*	0.62 (0.29–1.33) *0.22*	1.06 (0.50–2.27) *0.88*	0.50
Age *p-value*	1.06 (0.74–1.51) *0.76*	1.18 (0.70–1.99) *0.55*	0.97 (0.60–1.57) *0.91*	0.87
Short-term group *p-value*	1.06 (0.57–1.97) *0.86*	0.85 (0.44–1.65) *0.64*	0.56 (0.26–1.22) *0.14*	0.46
Home oxygen therapy *p-value*	2.84 (1.05–7.65) *0.04*	1.29 (0.54–3.08) *0.57*	1.08 (0.46–2.52) *0.86*	0.32
Active smokers *p-value*	0.70 (0.36–1.37) *0.30*	0.66 (0.28–1.57) *0.35*	0.61 (0.27–1.35) *0.22*	0.96
Pretreatment with systemic glucocorticoids *p-value*	1.33 (0.61–2.91) *0.47*	1.28 (0.53–3.10) *0.59*	1.93 (0.87–4.29) *0.11*	0.74
Hospitalisation >8 days *p-value*	1.51 (0.79–2.88) *0.21*	1.69 (0.82–3.47) *0.15*	1.64 (0.79–3.37) *0.18*	0.97
All variables listed in the table were simultaneously included in the model. * Chi^2-Test				

Table S3B: Multivariate analysis of re-exacerbation or re-exacerbation and/or death stratified by FEV_1 at discharge.

	FEV_1 (% pred.) ≥50% OR (95% CI)	**FEV_1 (% pred.) 30–49% OR (95% CI)**	**FEV_1 (% pred.) <30% OR (95% CI)**	**Heterogeneity p-value***
Re-exacerbation				
Women *p-value*	1.45 (0.67–3.15) *0.35*	0.52 (0.20–1.36) *0.19*	1.44 (0.44–4.67) *0.54*	0.23
Age *p-value*	0.81 (0.51–1.29) *0.38*	1.15 (0.58–2.28) *0.68*	1.01 (0.51–2.02) *0.97*	0.68
Short-term group *p-value*	1.11 (0.51–2.41) *0.80*	1.02 (0.41–2.56) *0.96*	0.74 (0.24–2.26) *0.60*	0.84
Home oxygen therapy *p-value*	1.90 (0.44–8.24) *0.39*	2.04 (0.51–8.19) *0.32*	0.77 (0.19–3.15) *0.72*	0.57
Active smokers *p-value*	0.43 (0.19–1.00) *0.05*	0.60 (0.19–1.87) *0.38*	0.53 (0.16–1.78) *0.30*	0.90
Pretreatment with systemic glucocorticoids *p-value*	1.00 (0.35–2.89) *1.00*	1.24 (0.33–4.59) *0.75*	2.44 (0.70–8.52) *0.16*	0.55

Table S3B (continued)				
Hospitalisation >8 days *p-value*	1.52 (0.69–3.38) *0.30*	1.77 (0.69–4.55) *0.24*	2.06 (0.70–6.07) *0.19*	0.91
Re-exacerbation and/or death				
Women *p-value*	1.06 (0.50–2.27) *0.88*	0.45 (0.17–1.19) *0.11*	1.31 (0.40–4.29) *0.66*	0.29
Age *p-value*	0.91 (0.58–1.43) *0.68*	1.15 (0.58–2.29) *0.69*	1.12 (0.56–2.24) *0.76*	0.81
Short-term group *p-value*	0.97 (0.46–2.07) *0.94*	0.88 (0.35–2.24) *0.79*	0.63 (0.21–1.95) *0.42*	0.82
Home oxygen therapy *p-value*	3.39 (0.74–15.4) *0.12*	3.05 (0.68–13.7) *0.15*	1.03 (0.25–4.23) *0.97*	0.45
Active smokers *p-value*	0.56 (0.25–1.24) *0.15*	0.53 (0.17–1.68) *0.28*	0.52 (0.15–1.76) *0.29*	0.99
Pretreatment with systemic glucocorticoids *p-value*	1.48 (0.55–4.03) *0.44*	0.98 (0.26–3.78) *0.98*	2.04 (0.58–7.15) *0.27*	0.74
Hospitalisation >8 days *p-value*	1.88 (0.87–4.08) *0.11*	2.18 (0.83–5.73) *0.11*	2.24 (0.76–6.66) *0.15*	0.96
All variables listed in the table were simultaneously included in the model. * Chi^2-Test				

Table S4A: Multivariate analysis of time to re-exacerbation or re-exacerbation and/or death stratified by gender.

	Women **HR (95% CI)**	**Men** **HR (95% CI)**	**Heterogeneity** **p-value***
Re-exacerbation			
Age *p-value*	1.16 (0.78–1.72) *0.47*	0.94 (0.68–1.30) *0.71*	0.42
Short-term group *p-value*	1.08 (0.56–2.09) *0.82*	0.84 (0.52–1.36) *0.48*	0.55
Home oxygen therapy *p-value*	1.44 (0.60–3.42) *0.41*	1.33 (0.66–2.69) *0.42*	0.90
Active smokers *p-value*	0.40 (0.21–0.79) *0.01*	0.82 (0.47–1.43) *0.48*	0.11
Pretreatment with systemic glucocorticoids *p-value*	1.34 (0.66–2.69) *0.42*	1.49 (0.78–2.82) *0.23*	0.83
Hospitalisation >8 days *p-value*	1.85 (0.92–3.70) *0.08*	1.39 (0.85–2.27) *0.19*	0.52

Table S4A (continued)			
FEV_1 (% predicted) discharge *p-value*	1.24 (0.81–1.90) *0.32*	1.31 (0.96–1.78) *0.09*	0.85
Re-exacerbation and/or death			
Age *p-value*	1.20 (0.81–1.78) *0.35*	0.98 (0.72–1.34) *0.92*	0.42
Short-term group *p-value*	1.03 (0.53–1.98) *0.93*	0.78 (0.49–1.23) *0.29*	0.50
Home oxygen therapy *p-value*	1.46 (0.61–3.46) *0.40*	1.63 (0.86–3.11) *0.13*	0.83
Active smokers *p-value*	0.44 (0.23–0.86) *0.02*	0.87 (0.52–1.49) *0.62*	0.12
Pretreatment with systemic glucocorticoids *p-value*	1.32 (0.66–2.64) *0.44*	1.61 (0.89–2.91) *0.12*	0.67
Hospitalisation >8 days *p-value*	1.89 (0.95–3.77) *0.07*	1.55 (0.97–2.48) *0.07*	0.64
FEV_1 (% predicted) discharge *p-value*	1.21 (0.80–1.85) *0.37*	1.16 (0.86–1.56) *0.33*	0.86
All variables listed in the table were simultaneously included in the model. * Chi^2-Test			

Table S4B: Multivariate analysis of re-exacerbation or re-exacerbation and/or death stratified by gender.			
	Women **OR (95% CI)**	**Men** **OR (95% CI)**	**Heterogeneity** **p-value***
Re-exacerbation			
Age *p-value*	1.12 (0.67–1.86) *0.68*	0.88 (0.58–1.33) *0.54*	0.47
Short-term group *p-value*	1.25 (0.53–2.99) *0.61*	0.88 (0.47–1.64) *0.69*	0.52
Home oxygen therapy *p-value*	1.17 (0.30–4.54) *0.82*	1.57 (0.61–4.06) *0.35*	0.73
Active smokers *p-value*	0.27 (0.10–0.69) *0.01*	0.73 (0.36–1.47) *0.38*	0.10
Pretreatment with systemic glucocorticoids *p-value*	1.57 (0.56–4.40) *0.39*	1.17 (0.50–2.71) *0.72*	0.66
Hospitalisation >8 days *p-value*	2.48 (1.02–6.05) *0.045*	1.43 (0.76–2.67) *0.27*	0.32

Table S4B (continued)			
FEV1 (% predicted) discharge *p-value*	1.63 (0.92–2.89) *0.10*	1.55 (1.04–2.31) *0.03*	0.89
Re-exacerbation and/or death			
Age *p-value*	1.19 (0.72–1.99) *0.49*	0.94 (0.62–1.43) *0.77*	0.47
Short-term group *p-value*	1.12 (0.48–2.66) *0.79*	0.74 (0.40–1.38) *0.34*	0.44
Home oxygen therapy *p-value*	1.24 (0.32–4.76) 0.76	2.74 (1.02–7.38) 0.046	0.35
Active smokers *p-value*	0.32 (0.13–0.80) *0.02*	0.75 (0.37–1.52) *0.43*	0.15
Pretreatment with systemic glucocorticoids *p-value*	1.48 (0.54–4.10) *0.45*	1.34 (0.58–3.13) *0.50*	0.88
Hospitalisation >8 days *p-value*	2.59 (1.07–6.24) *0.03*	1.76 (0.95–3.28) *0.07*	0.49
FEV_1 (% predicted) discharge *p-value*	1.55 (0.88–2.73) *0.13*	1.32 (0.89–1.97) *0.17*	0.65
All variables listed in the table were simultaneously included in the model. * Chi^2-Test			