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Clinical characteristics governing treatment adjustment in COPD patients: results from the Swiss COPD cohort study

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Summary

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a widespread chronic disease characterised by irreversible airway obstruction [1]. Features of clinical practice and healthcare systems for COPD patients can vary widely, even within similar healthcare structures. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy is considered the most reliable guidance for the management of COPD and aims to provide treating physicians with appropriate insight into the disease. COPD treatment adaptation typically mirrors the suggestions within the GOLD guidelines, depending on how the patient has been categorised. However, the present study posits that the reasons for adjusting COPD-related treatment are hugely varied.

OBJECTIVES: The objective of this study was to assess the clinical symptoms that govern both pharmacological and non-pharmacological treatment changes in COPD patients. Using this insight, the study offers suggestions for optimising COPD management through the implementation of GOLD guidelines.

METHODS: In this observational cohort study, 24 general practitioners screened 260 COPD patients for eligibility from 2015–2019. General practitioners were asked to collect general information from patients using a standardised questionnaire to document symptoms. During a follow-up visit, the patient's symptoms and changes in therapy were assessed and entered into a central electronic database. Sixty-five patients were removed from the analysis due to exclusion criteria, and 195 patients with at least one additional visit within one year of the baseline visit were included in the analysis. A change in therapy was defined as a change in either medication or non-medical treatment, such as pulmonary rehabilitation. Multivariable mixed models were used to identify associations between given symptoms and a step up in therapy, a step down, or a step up and a step down at the same time.

RESULTS: For the 195 patients included in analyses, a treatment adjustment was made during 28% of visits. In 49% of these adjustments, the change in therapy was a step up, in 33% a step down and in 18% a step up (an increase) of certain treatment factors and a step down (a reduction) of other prescribed treatments at the same time. In the multivariable analysis, we found that the severity of disease was linked to the probability of therapy adjustment: patients in GOLD Group C were more likely to experience an increase in therapy compared to patients in GOLD Group A (odds ratio [OR] 3.43 [95% confidence interval {CI}: 1.02–11.55; p = 0.135]). In addition, compared to patients with mild obstruction, patients with severe (OR 4.24 [95% CI: 1.88–9.56]) to very severe (OR 5.48 [95% CI: 1.31–22.96]) obstruction were more likely to experience a therapy increase (p <0.0001). Patients with comorbidities were less likely to experience a treatment increase than those without (OR 0.42 [95% CI: 0.24–0.73; p = 0.002]). A therapy decrease was associated with both a unit increase in COPD Assessment Test (CAT) score (OR 1.07 [95% CI: 1.01–1.14; p = 0.014]) and having experienced an exacerbation (OR 2.66 [95% CI: 1.01–6.97; p = 0.047]). The combination of steps up as well as steps down in therapy was predicted by exacerbation (OR 8.93 [95% CI: 1.16–68.28; p = 0.035]) and very severe obstruction (OR 589 [95% CI: 2.72 – >999; p = 0.109]).

CONCLUSIONS: This cohort study provides insight into the management of patients with COPD in a primary care setting. COPD Group C and airflow limitation GOLD 3–4 were both associated with an increase in COPD treatment. In patients with comorbidities, there were often no treatment changes. Exacerbations did not make therapy in-

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creases more probable. The presence of neither cough/sputum nor high CAT scores was associated with a step up in treatment.

Introduction

Chronic obstructive pulmonary disease (COPD) is a widespread chronic disease and places a major burden on patients and healthcare systems. The disease is an increasing cause of morbidity and mortality, in contrast to other major chronic diseases [2]. With a global prevalence of approximately 11.7%, COPD is considered the fourth leading cause of death worldwide [3]. COPD is also associated with a significant economic burden by producing an annual cost of nearly 50 billion Euros in the EU [2]. COPD is a major problem globally because of increasing tobacco consumption and pollution along with ageing of the world's population [4].

In response to the burden of COPD, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) created guidelines to help optimise the treatment of COPD, increase awareness of the disease and decrease morbidity and mortality. The GOLD guidelines provide advice on how to optimise COPD prevention, diagnosis and treatment [5].

A COPD diagnosis is made according to the patient's established medical history. In this longitudinal cohort study, the physician noted each patient's medical history and conducted a medical examination. All patients were asked to complete the COPD Assessment Test (CAT) questionnaire. The COPD Assessment Test score was calculated by summing the points for each variable. This resulted in a CAT score of 0–40, classified into four groups ranging from low to very high, depending on the level of impact of the disease on the person's health. Patients in this cohort study were typically categorised depending on the severity of airflow limitation, the number of exacerbations within the last year and the current impact of symptoms, as assessed by the CAT score. Depending on the severity of airway obstruction, patients were assigned GOLD 1, 2, 3 or 4. This categorisation would then aid the physician's diagnosis and treatment of the patient in question. In a revision of the GOLD guidelines in 2017, a refinement of the ABCD tool was proposed, separating spirometric grades from the ABCD groups. In this refined assessment scheme, patients should undergo spirometry to determine the severity of airflow limitation and then undergo an assessment of either dyspnea using the modified Medical Research Council dyspnea scale (mMRC) or symptoms using COPD Assessment Test. The history of exacerbations should also be recorded.

Pharmacological treatments according to GOLD 2017 recommendations were defined as follows:

- Group A: short-acting beta-agonist (SABA) or short-acting muscarinic antagonist (SAMA)
- Groups B and C: long-acting beta-agonist (LABA), long-acting muscarinic antagonist (LAMA) or LAMA/LABA combination
- Group D: any treatment regimen including LAMA/LABA combination

While guidelines are essential for the standardisation of disease, clinical practice often differs from proposed treatment recommendations [6]. Therefore, this study sought to gain insight into the factors governing a physician's decision to adjust therapy for COPD patients.

The under- and over-diagnosis of COPD in the primary healthcare sector likely contribute to the increase in morbidity and mortality associated with this disease. It remains unclear how much the integration of GOLD guidelines affects the clinical outcomes of COPD patients. Although patient-reported outcome questionnaires like the CAT and the mMRC are necessary to assess the severity of the disease and to categorise patients correctly so that they receive the recommended treatments, it seems that a majority of physicians in real practice settings do not use these questionnaires [3]. This might lead to physicians underestimating symptoms and thus not adjusting therapy as might be necessary. Several cases of misdiagnosis have been noted in Switzerland, including in patients who have been diagnosed with COPD but have not fulfilled the GOLD criteria [2]. Patients with COPD are typically not referred to specialists as often as are patients with other chronic conditions, such as diabetes or chronic heart disease. Therefore, to accurately assess the prevalence of COPD, it is necessary to gain better insight into the management of COPD therapy, which typically falls to the primary care sector.

Hypothesis and main goals

The focus of this study was gaining insight into the management of COPD therapy within the primary care sector. More specifically, the goal of the study was to investigate factors associated with changes in COPD therapy.

Materials and methods

This project used data from the Swiss COPD Cohort Study, which is an ongoing, multicentric, population-based study with the aim of assessing COPD management within the primary care setting. Participants have been recruited since 2007. The present study focused on patients recruited from 2015–2019. General practitioners from Switzerland were invited to join the study. In total, 24 general practitioners participated in the Swiss COPD Cohort Study. The ethics committees of all cantons involved permitted the study (EK Nr. 170/06). The 24 general practitioners were asked to invite all patients with mild to severe COPD (GOLD stages 1–4) to participate in the study. All patients included in the study provided informed consent. There was an initial study examination (baseline visit), followed by re-examinations every 6 months. The inclusion criteria were as follows:

- FEV1/FVC <70% after inhalation of a bronchodilator
- age >40 years
- smoker or ex-smoker of at least 20 pack-years
- informed consent

During the baseline visit, general information, like age, sex, weight, height, year of first diagnosis of COPD, smoking status, number of attempts to stop smoking and pack-years, was assessed. General practitioners used a standardised questionnaire to document symptoms by assessing the CAT score and mMRC, comorbidities, exacerbations, spirometry and treatment. The following comorbidities were evaluated using the questionnaire: asthma, cardiovas-

cular diseases (coronary heart disease, heart failure, peripheral artery disease, hypertension and cerebrovascular insult), diabetes and malignant diseases.

General practitioners then conducted a spirometric assessment according to European Respiratory Society (ERS) / American Thoracic Society (ATS) technical standards on interpretative strategies for routine lung function tests [7]. They documented the forced expiratory volume in 1 second (FEV1) in litres; FEV1 percentage of the reference value and/or lower limit of normal; forced vital capacity (FVC) in litres; FVC percentage of the reference value and/or lower limit of normal; and FEV1/FVC (%) (Tiffeneau index). During follow-up visits, patients' symptoms were evaluated by assessing the CAT score and mMRC [4, 5] and by asking about medication, non-pharmacological treatments, hospitalisation and exacerbations. Undesired changes were defined as a worsening of symptoms that may have required a change in therapy.

The patients' data were anonymised and were entered upon collection into a central electronic database (RDE Light) by the study team. Patients with at least one additional visit within one year of the baseline visit were included. Patients with a change in therapy were signalled to the study team, in line with the study's objective. Our primary outcome was a change in therapy, which was defined as a change in either medication (± medication) or non-medical treatment, such as pulmonary rehabilitation. A change in medication was only counted if there was a change of substance class; i.e., a change within one substance class was not regarded as a change in therapy. Adjustments to therapy were categorised into three groups: step up in therapy, step down, and step up and step down at the same time. An example of a step up and step down at the same time is the new prescription of a long-acting muscarinic antagonist while treatment with a short-acting beta-agonist was stopped. For those patients for whom a change in treatment was detected, we sought to establish factors associated with the treatment adjustment.

Statistical analysis

Data were summarised using descriptive statistics (mean ± standard deviation for continuous data, absolute and relative frequencies for categorical data). The effects of disease characteristics on treatment change were analysed using separate univariable and multivariable logistic mixed models. These models included the following as independent variables: the disease characteristic (as a fixed effect) and the patient (as a random effect). We excluded mMRC from the multivariable regression because of its close association with GOLD groups. The effect of the disease characteristic on the change in treatment was calculated as an odds ratio (OR) with a 95% confidence interval (CI). The hypothesis of no effect was evaluated using the Wald test. *P*-values were interpreted in a descriptive sense.

Data analysis was conducted according to the standard operating procedures of the Clinical Trials Unit, University Medical Centre Freiburg. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc.). For descriptive analyses, the procedures FREQ and MEAN were used. For the generalised mixed models, the procedure GLIMMIX was used. Analytical code is available from the authors upon reasonable request.

Ethical approval and consent to participate

We received ethical approval for this study by the local ethical committee (Ethikkommission Nordwest- und Zentralschweiz [EKNZ], formerly Ethikkommission beider Basel [EKBB]) in 2017 (EK Nr. 170/06)and subsequently by ethical committees of all other participating Swiss cantons. ClinicalTrials.gov Identifier: NCT02065921.

All participants provided written consent to participate in the study.

Results

During the study period, we recruited 260 patients, 253 of whom had received a spirometry diagnosis of COPD. A total of 48 patients were excluded from the study because they were missing an additional visit after the baseline visit or their visits were more than 1 year apart. A further 10 patients were excluded because of missing information on medication (figure 1).

In total, patients made 690 visits. There were 500 visits that did not result in a change in therapy and 190 visits that resulted in a change in drug therapy (table 2). The table shows the odds ratios for predictors of change in therapy. The majority of therapy adjustments were to medication. Only 9.2% of the patients received pulmonary rehabilitation at any point within the study period. The changes in therapy were categorised into three groups, namely a step up in treatment, a step down, and a step up and a step down at the same time. During 72% of the visits, no treatment adjustments were made. In those cases, medication was not changed, and no pulmonary rehabilitation was prescribed. During 28% (190) of the visits, general practitioners modified medication or prescribed pulmonary rehabilitation. For 94/190 visits (49.5%) with a change in treatment, there was a step up in therapy, whereas in 62/190 cases (32.6%) there was a step down in therapy. In the remaining 34/190 cases (17.9%), there were both a step up and a step down in medication during one visit. Furthermore, we observed that 32.6% of the overall population received a clinical diagnosis of COPD that could not be confirmed by spirometry.

Therapy increase

In the multivariable analysis, we found that the severity of disease was linked to the probability of experiencing a therapy increase: patients in GOLD Group C were more likely to experience an increase in therapy compared to patients in GOLD Group A (OR 3.34 [95% CI: 1.02–11.55; p = 0.013]). Also, compared to patients with mild obstruction, patients with severe (OR 4.24 [95% CI: 1.88–9.56]) and very severe (OR 5.48 [95% CI: 1.31–22.96]) obstruction were more likely to experience a therapy increase (p <0.0001). Comorbidities were negatively associated with increases in therapy (OR 0.42 [95% CI: 0.24–0.73; p = 0.002]) (table 3).

Therapy decrease

GOLD Group C was also associated with a therapy decrease (OR 9.23 [95% CI: 2.31–36.85; p = 0.0045]). The

Figure 1: Study population. Summary of changes in treatment.

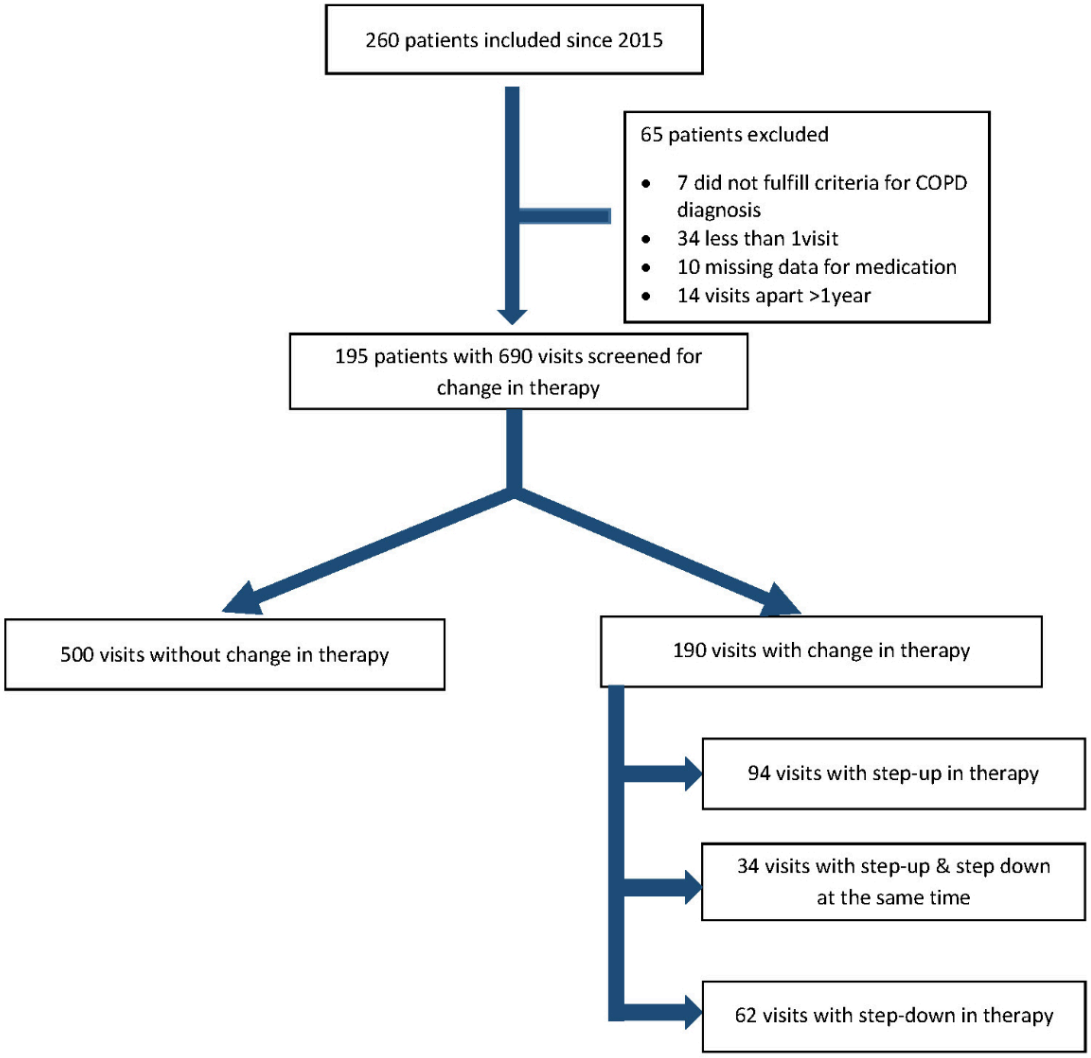

Table 1:
Baseline characteristics.

General characteristics		Study population
Age (years)		68.1 (±9.82)
Female sex		69 (35.38%)
Smoking status	Current smoker	92 (47.18%)
	Ex-smoker	99 (52.66%)
Tobacco history (pack-years)		47.0 (±19.8)
GOLD classification	GOLD A	79 (40.51%)
	GOLD B	80 (41.03%)
	GOLD C	16 (8.21%)
	GOLD D	20 (10.26%)
GOLD stage	1 (FEV1 ≥80% predicted)	31 (15.98%)
	2 (FEV1 50–79% predicted)	107 (55.15%)
	3 (FEV1 30–49% predicted)	47 (24.23%)
	4 (FEV1 <30% predicted)	9 (4.64%)
FEV1		60.9% (±18.13%)
Tiffeneau index		56.9% (±10.24%)
Any comorbidity		139 (71.28%)
Cough/sputum		120 (64.52%)

FEV1: forced expiratory volume in 1 second; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

severity of airflow limitation was not associated with steps down in medication. Exacerbation was positively associated with a decrease in treatment (OR 2.66 [95% CI: 1.01–6.97; p = 0.0471]). A higher COPD Assessment Test score was mildly associated with a step down in medication (OR 1.07 [95% CI: 1.01–1.14; p = 0.014]). Comorbidities were not associated with a step down in therapy. Neither cough nor sputum showed an association with therapy decrease (table 4).

Therapy increase and decrease at the same time

Visits with a step up *and* step down at the same time were strongly associated with both very severe airflow limitation (OR 589 [95% CI: 2.72 – >999; p = 0.1092]) and exacerbation (OR 8.93 [95% CI: 1.17–68.28; p = 0.0349]). Neither GOLD group, CAT score nor the presence of cough and/or sputum was associated with both a therapy increase and decrease during one visit (table 5).

Table 2:
Predictors of a change in therapy (n = 620).

Factor	Effect	Odds ratio	Lower 95% CL	Upper 95% CL	p-value
CAT	Unit change of CAT from mean	1.012	0.975	1.051	0.5134
Comorbidities	Yes vs no	0.634	0.405	0.991	0.0455
Coughand/or sputum	Cough vs none	0.937	0.472	1.858	0.9821
	Cough/sputum vs none	0.968	0.560	1.674	–
Exacerbation	Yes vs no	1.656	0.823	3.330	0.1566
GOLD	GOLD B vs A	1.028	0.637	1.658	0.0416
	GOLD C vs A	4.045	1.410	11.605	–
	GOLD D vs A	0.723	0.279	1.871	–
GOLD FEV1	Moderate vs mild	0.812	0.470	1.402	0.0003
	Severe vs mild	2.290	1.191	4.400	–
	Very severe vs mild	4.384	1.358	14.153	–

CL: confidence level; FEV1: forced expiratory volume in 1 second; mMRC: modified Medical Research Council dyspnea scale; CAT: COPD Assessment Test

Table 3:
Predictors of an increase in therapy (n = 540).

Factor	Effect	Odds ratio	Lower 95% CL	Upper 95% CL	p-value
CAT	Unit change of CAT from mean	0.992	0.945	1.041	0.7395
Comorbidities	Yes vs no	0.421	0.243	0.728	0.0020
Cough and/or sputum	Cough vs none	1.380	0.597	3.191	0.6962
	Cough/sputum vs none	1.288	0.638	2.599	–
Exacerbation	Yes vs no	0.784	0.279	2.203	0.6435
GOLD	GOLD B vs A	0.827	0.447	1.532	0.1345
	GOLD C vs A	3.341	1.019	11.553	–
	GOLD D vs A	0.803	0.255	2.532	–
GOLD FEV1	Moderate vs mild	0.997	0.478	2.079	<0.0001
	Severe vs mild	4.239	1.879	9.564	–
	Very severe vs mild	5.484	1.310	22.960	–

CL: confidence level; FEV1: forced expiratory volume in 1 second; mMRC: modified Medical Research Council dyspnea scale; CAT: COPD Assessment Test

Table 4:
Predictors of a decrease in therapy (n = 508).

Factor	Effect	Odds ratio	Lower 95% CL	Upper 95% CL	p-value
CAT	Unit change of CAT from mean	1.073	1.014	1.135	0.0140
Comorbidities	Yes vs no	0.803	0.387	1.663	0.5530
Cough and/or sputum	Cough vs none	0.795	0.261	2.420	0.2842
	Cough/sputum vs none	0.498	0.207	1.194	–
Exacerbation	Yes vs no	2.657	1.013	6.972	0.0471
GOLD	GOLD B vs A	1.091	0.485	2.454	0.00045
	GOLD C vs A	9.226	2.310	36.854	–
	GOLD D vs A	0.511	0.106	2.463	–
GOLD FEV1	Moderate vs mild	0.633	0.267	1.499	0.1045
	Severe vs mild	1.766	0.668	4.673	–
	Very severe vs mild	0.855	0.126	5.803	–

CL: confidence level; FEV1: forced expiratory volume in 1 second; mMRC: modified Medical Research Council dyspnea scale; CAT: COPD Assessment Test

Discussion

This cohort study has provided deeper insight into how patients with COPD are treated in primary care settings. COPD Group C and severe to very severe airflow limitation were both associated with an increase in COPD treatment. Patients with comorbidities were more likely to have received no treatment changes. Past COPD exacerbations were not associated with therapy increases.

The fact that GOLD Group C patients were more likely to see a step up in treatment compared to GOLD A patients seemed consistent with expectations for clinical practice. This is because patients in GOLD Group C are affected more by the disease, as they experience more exacerbations, although they do not have more symptoms between exacerbations than do GOLD Group A patients. A therapy decrease was associated with GOLD Group C and the presence of exacerbations. This result was rather unexpected, as a therapy increase is expected in the case of more severe disease. That is, GOLD Group A or B is expected to be associated with a step down in therapy. There were no concrete associations between GOLD Group D and a change in therapy, likely due to the small number of patients in that group. Patient Group C was the smallest of our study. The size of GOLD Groups A–D can differ depending on the questionnaire used. COPD Assessment Test and mMRC correlate with each other; however, the inter-rater agreement between CAT and mMRC is quite good [8]. That might be a reason why patient Group C was associated with a treatment increase as well as a treatment decrease in our study. The newest COPD GOLD guidelines propose to merge groups C and D into a single group E [9]. This suggests that frequent exacerbators with few symptoms (Group C) should receive the same treatment as frequent exacerbators with high symptom load (Group D). Together with our finding that Group C was associated with all different types of therapy changes, this may imply that Group C is very difficult to treat satisfactorily. The newest GOLD suggestions may help in treating this particular patient group.

Our results showed that exacerbation was not strictly associated with an increase in therapy provided by general practitioners, which was unexpected. Other studies have reported positive associations [10, 11]. Campos et al. considered the prescribed treatment during a routine follow-up visit for COPD treatment. The results indicated that the majority of doctors did not change the patient's treatment regimen. Among those whose therapeutic regimen changed, disease exacerbation was the main driver of increased treatment [11]. Although mMRC and the patient's CAT score serve as indicators for assessment and (change in) treatment, our study did not find them to be associated with changes in therapy. The study noted that the presence of comorbidities made treatment changes less likely. This is highly interesting and relevant, as 71.3% of patients had comorbidities. We had expected the comorbidities to lead to therapy adjustments, as comorbidities potentially cause worsened COPD-related symptoms, like dyspnea, and more suffering due to the disease. Overington et al. explain such circumstances with presumed barriers to implementing guidelines, including factors such as lack of familiarity amongst clinicians with guidelines and inadequate implementation programs [12]. In patients with multimorbidity, an increase in dyspnea, and therefore in COPD Assessment Test or mMRC, is not necessarily caused by COPD itself. It is possible that physicians judged the increase in symptoms as not being related to lung disease [13].

Patient-reported questionnaires like the COPD Assessment Test and mMRC are necessary to assess the severity of the disease and to group patients correctly so that they receive the recommended treatment. However, a majority of physicians in real practice settings do not use these questionnaires [14]. That might lead to physicians underestimating symptoms and thus not adjusting the therapy, as they perhaps should be doing. Studies such as Wang et al. have confirmed that that the prevalence of excess polypharmacy increases with age, thereby increasing the risk of various clinical outcomes. This study assumed that general practitioners hesitate to adjust treatment in COPD patients due to these potential side effects, as suggested by studies in the field [14]. Other suggested reasons for this hesitation were a potential lack of time or even patient hesitancy in changing medication. Therefore, this study suggested further educational efforts to disseminate knowledge of GOLD guidelines to improve the implementation of COPD management recommendations.

Our data showed that a number of patients were diagnosed with COPD without fulfilling spirometric criteria and even had treatment adjusted (step up or step down), only partially in line with GOLD suggestions. This somewhat *ad hoc* implementation of GOLD guidelines for COPD man-

Table 5:
Predictors of both an increase and decrease in therapy (n = 492).

Factor	Effect	Odds ratio	Lower 95%CL	Upper 95% CL	p- value
CAT	Unit change of CAT from mean	0.889	0.766	1.033	0.1239
Comorbidities	Yes vs no	1.857	0.309	11.153	0.4975
Cough and/or sputum	Cough vs none	0.133	0.009	2.208	0.1909
	Cough/sputum vs none	1.737	0.196	15.410	–
Exacerbation	Yes vs no	8.932	1.168	68.280	0.0349
GOLD	GOLD B vs A	0.727	0.094	5.627	0.6062
	GOLD C vs A	<0.001	–	–	–
	GOLD D vs A	0.054	<0.001	16.649	–
GOLD FEV1	Moderate vs mild	1.563	0.249	9.795	0.1092
	Severe vs mild	1.549	0.059	40.664	–
	Very severe vs mild	589.266	2.719	>999.999	–

CL: confidence level; FEV1: forced expiratory volume in 1 second; mMRC: modified Medical Research Council dyspnea scale; CAT: COPD Assessment Test

agement in a primary care setting is the focus of Sehl et al.'s literature review of adherence to COPD management guidelines in general practice [15]. Sehl et al. showed variability in which parts of the guidelines general practitioners adhered to. One of the most commonly cited gaps in adherence was the omission of spirometry. Spirometry is essential and required to confirm a COPD diagnosis [10]. The omission is therefore contrary to the GOLD guidelines [16].

The data presented in our study tend to agree with similar studies that have investigated the working integration of GOLD guidelines into COPD management in the primary care sector. Studies such as that of Marmy et al. reached similar conclusions to our study, for example by reporting that up to 53% of COPD patients in their study group were not consistently treated according to GOLD 2017 recommendations [3]. Jochmann et al. also highlighted the manner in which COPD treatment in primary care tends to differ from proposed GOLD treatment options [17]. This study raised the issue of general practitioners not using the COPD Assessment Test questionnaire, which is recommended by the GOLD guidelines for an adequate assessment of patients. Similarly, Jochmann et al. highlighted a lack of the spirometry that should be performed on a routine basis [17]. A further study by Urwyler et al. underlined the importance of fulfilling spirometric criteria. Since all spirometry tests are administered by the respective primary physician, we were unable to account for this bias. The results of this study raise the question of the extent of GOLD guideline knowledge and suggest the need for more detailed knowledge dissemination among general practitioners [18]. Grewe et al. found that the prescription of medicine with treatment adjustment was not as would be considered suitable for the patient's symptoms and was only partially compliant with GOLD guidelines. Patients with more severe COPD were more likely to be treated according to the guidelines, which resulted in a low rate of adherence therapy (59.1%), in line with the results of other studies [19]. This study noted the general lack of concrete data on COPD management with general practitioner surgeries, which would provide valuable insight on the subject.

Conclusion

The authors note the following weaknesses of the present study. This project is likely to have drawn some inaccurate conclusions due to some inconclusive data. Some patients had to be excluded due to missing/inconclusive data. Furthermore, patients who did not attend a follow-up visit were excluded from the analysis, which may have resulted in bias. The patients that were recruited by the general practitioner participated in the study voluntarily, which could have resulted in a selection bias leading to a sample unrepresentative of the population. This study did not ask the physicians involved for the motivations behind their actions, which may be an interesting area for further study.

Data availability statement

The datasets used and analysed in this study are available from the corresponding authors upon reasonable request.

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Author contributions: LK: Conception of study and design, interpretation of data, acquisition and analysis of data and contributing to the manuscript. ZP: Writing consequent drafts of the manuscript. NAH, POB, PNC: acquisition of data, support for the participants. TG, LJZ, MK, SM, DM, MT, RT, CvG: Contributions to the conception of the study, analysis and interpretation of the data, contributions to the manuscripts. JDL: Responsible principle investigator, supervision of acquisition of data, contributions to the manuscript.

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Potential competing interests

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