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Deterioration and Mortality Risk of COPD Patients Not Fitting into Standard GOLD Categories: Results of the COSYCONET Cohort

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Abstract

Background: Patients with COPD-specific symptoms and history but FEV_1/FVC ratio ≥0.7 are a heterogeneous group (former GOLD grade 0) with uncertainties regarding natural history. ***Objective:*** We investigated which lung function measures and cutoff values are predictive for deterioration according to GOLD grades and all-cause mortality. ***Methods:*** We used visit 1–4 data of the COSYCONET cohort. Logistic and Cox regression analyses were used to identify relevant parameters. GOLD 0 patients were categorized according to whether they maintained grade 0 over the following 2 visits or deteriorated persistently into grades 1 or 2. Their clinical characteristics were compared with those of GOLD 1 and 2 patients. ***Results:*** Among 2,741 patients, 374 GOLD 0, 206 grade 1, and 962 grade 2 patients were identified. GOLD 0 patients were characterized by high symptom burden, comparable to grade 2, and a restrictive lung function pattern; those with FEV_1/FVC above 0.75 were unlikely to deteriorate over time into grades 1 and 2, in contrast to those with values between 0.70 and 0.75. Regarding mortality risk in GOLD 0, FEV_1%predicted and age were the relevant determinants, whereby a cutoff value of 65% was superior to that of 80% as proposed previously. ***Conclusions:*** Regarding patients of the former GOLD grade 0, we identified simple criteria for

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FEV_1/FVC and FEV_1% predicted that were relevant for the outcome in terms of deterioration over time and mortality. These criteria might help to identify patients with the typical risk profile of COPD among those not fulfilling spirometric COPD criteria.

Introduction

Chronic obstructive pulmonary disease (COPD) shows a high prevalence worldwide and is expected to contribute to the morbidity and mortality burden even more in future [1]. There are international expert recommendations for diagnosis and treatment, particularly by the GOLD consortium [2]. In these recommendations, the diagnosis includes spirometric lung function. In case of the ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) being <0.7, the spirometric condition for COPD is met. These patients are then further categorized into grades 1 to 4 according to FEV_1% predicted [2]. There are, however, also patients with functional and clinical characteristics of COPD who do not fulfill the FEV_1/FVC criterion. These patients have previously been categorized as "grade 0" or "at risk" [3], and a number of studies have shown that these patients have respiratory disease and are prone to exacerbations and hospital admissions [4]. Their characteristics can appear as an extrapolation of grade 1–4 patients towards normal [3]. Although the formal category "grade 0" is not in common use, the group seems to be clinically interesting and relevant [5, 6]. This has been underlined by a recent analysis, in which patients with FEV_1/FVC ≥ 0.7 were subcategorized according to FEV_1, patients with FEV_1 < 80% predicted were categorized as "preserved ratio impaired spirometry" (PRISm), and it was shown that these patients were at risk regarding hospitalizations and mortality [7]. This emphasizes the heterogeneity within the grade 0 group.

Patients who do not fit into the GOLD 1–4 grading are not rare in clinical practice and often treated with COPD medications [6]. Their actual categorization is affected by the changes and variability of spirometric values over time, as indicated by a previous study [8]. We recently analyzed the distribution of respiratory medication and its relationship to GOLD recommendations in GOLD grades 1–4 [6], using data of the COPD cohort COSYCONET. This cohort also comprises a considerable number of patients with the diagnosis of COPD but FEV_1/FVC ≥ 0.7 at study entry, with the presence of symptoms (i.e., former GOLD grade 0) [9]. The present analysis addressed the question of which characteristics of grade 0 patients predict changes over time into higher spirometric grades and which parameters are relevant for mortality. For this purpose, data from 3 visits covering 1.5 years of follow-up time were analyzed. Moreover, baseline characteristics were compared to those of GOLD grade 1 or 2 patients.

Methods

Study Population

COSYCONET is a multicenter COPD cohort study initiated in 31 study centers [10]. Visit 1, visit 2 (6 months after inclusion), and visit 3 (18 months after inclusion) as well as visit 4 data (36 months after inclusion) from this cohort were analyzed [9]. Patients with initial GOLD grade 0 were identified based on their lung function showing FEV_1/FVC ≥ 0.7 in the presence of symptoms of chronic bronchitis. Patients with FEV_1/FVC ≥ 0.7 but without symptoms of chronic bronchitis were excluded. Patients with GOLD grades 1 and 2 were used to compare clinical characteristics at baseline. The study was approved by the respective ethical committees, and all patients gave their written informed consent.

Assessments

All assessments were performed by using the study protocol documented previously [9]. Lung function assessments included spirometry, body plethysmography, and diffusing capacity, whereby predicted values were predicted by GLI [11, 12] or ESCS [13]. GOLD grades 1–4 [14] were based on GOLD recommendations, as well as the GOLD groups A–D based on the modified Medical Research Council dyspnea score (mMRC) [14]. Assessment of comorbidities was performed by structured interviews, and based on reported physician-based diagnosis [9], this was extended, where possible, by the presence of disease-specific medication [15, 16]. Patients were asked to bring all their medication at each study visit. Mortality assessment was based on the follow-up time of 3 years (visit 4) in analogy to a previous approach [17, 18]. We also adopted the subcategorization according to PRISm into which COPD patients with FEV_1/FVC ≥ 0.7 were classified if their FEV_1% predicted was below 80% [7].

Statistical Analysis

We used mean values and standard deviations for data descriptions. Comparison between groups was performed by ANOVA with post hoc comparisons according to Duncan. To evaluate the stability of GOLD grades over time, the following approach was taken. Patients remaining in grade 0 in visits 1–3 were contrasted with patients showing grade 0 at visit 1 and grades 1 or 2 at visits 2 and 3, without grade 0 reappearing. Patients changing to grades 3 and 4 were omitted in order to avoid a bias due to either COPD superdecliners or measurement errors. Patients with reappearing grade 0 were also omitted from the longitudinal comparisons, since they did not show a consistent change over time. Thus, only the 2 well-defined groups were studied, that is, patients remaining stable in grade 0 or declining to grade 1 or 2 during follow-up. An analogous approach was followed for patients showing grade 1 at

Table 1. The baseline characteristics of grade 0, 1, and 2 patients

	GOLD 0	GOLD 1	GOLD 2
Gender, m/f*	185/189$^{\$,\&}$	124/82	579/383
Age, years	64.85±9.7	66.20±8.7	65.68±8.5
BMI, kg/m^2*	29.02±5.8$^{\$,\&}$	26.64±4.6	27.42±5.1
Pack-years*	40.13±35.8$^{\&}$	45.07±31.2	50.96±37.7
FEV_1% predicted*	80.36±19.2$^{\$,\&}$	88.62±8.1	62.69±8.3
FVC% predicted*	80.99±18.3$^{\$,\&}$	106.81±10.8	86.32±12.9
FEV_1/FVC% predicted*	99.02±6.9$^{\$,\&}$	82.78±5.6	73.15±10.2
ITGV% predicted*	110.18±25.4$^{\$,\&}$	127.76±24.8	135.48±27.6
RV% predicted*	125.58±33.8$^{\$,\&}$	133.21±32.4	151.01±38.1
RV/TLC %	0.46±0.1$^{\$,\&}$	0.42±0.1	0.49±0.1
TLCO% predicted*	76.26±20.9$^{\&}$	75.99±23.3	62.88±19.5
KCO% predicted*	86.02±21.1$^{\$,\&}$	74.15±21.9	69.05±21.5
6-MWD, m*	437.94±113.6$^{\$}$	486.90±86.8	443.08±93.8
CAT*	18.11±7.0$^{\$}$	14.24±6.8	16.89±7.1
mMRC*	1.31±0.9$^{\$}$	0.99±0.7	1.35±0.8
VAS*	59.19±17.5$^{\$}$	67.16±16.9	61.45±18.1
GOLD ABCD mMRC*	179 (47.9%)/71 (19.3%)/ 66 (17.6%)/55 (14.7%)$^{\$}$	145 (70.4%)/29 (14.1%)/ 23 (11.2%)/8 (3.9%)	481 (50.0%)/201 (20.9%)/ 139 (14.4%)/137 (14.2%)
GOLD BD symptoms*	127 (34.1%)$^{\$}$	37 (18.0%)	338 (35.3%)
GOLD CD exacerbations*	121 (32.5%)$^{\$}$	31 (15.1%)	276 (28.8%)

Values given are mean values and standard deviation, except for mMRC for which median values and quartiles are given. All parameters listed in the table were significantly different ($p < 0.001$ each) between groups except for age which was not significant. FEV_1, forced expiratory volume; FVC, forced vital capacity; mMRC, modified Medical Research Council dyspnea score. The statistical comparisons were performed by χ^2 tests of contingency tables for gender, mMRC, and GOLD ABCD and by one-way ANOVA for all other parameters. * Significantly ($p < 0.001$) different between groups. $^{\$}$ Significantly ($p < 0.01$) different from GOLD 1. $^{\&}$ Significantly ($p < 0.01$) different from GOLD 2 with post hoc comparisons according to Duncan, or pairwise comparisons using the respective contingency subtables.

visit 1; in these patients, deteriorations comprised GOLD grades 2–4. Logistic regression analyses were used to identify risk factors for deterioration of GOLD grades over time, and Cox proportional hazard regression analysis was used to identify risk factors of mortality. Receiver operating characteristics (ROC analyses) and the Youden Index were used to identify optimal cutoff points. As usual, significance was assumed for $p < 0.05$. The assessments were performed using SPSS Statistics 23 (IBM Corp., Armonk, NY, USA).

Results

Study Cohort

Within COSYCONET, 2,741 patients were included [9], of whom 450 could not be categorized into GOLD stages 1–4. Of these, 76 patients did not report symptoms of chronic bronchitis at the time of the study, whereas the other 374 patients did. Following the initial definition of GOLD "grade 0" [19], we considered only the latter ones as eligible for the present analysis. GOLD grade 1 and 2 patients were defined according to recent criteria [14] comprising 206 and 962 patients, respectively, and were used for the comparison of baseline characteristics.

Functional and Clinical Results

The baseline characteristics of grade 0 patients are given in Table 1, together with data for grades 1 and 2. All parameters except age differed significantly ($p < 0.001$, ANOVA) between the 3 grades. According to post hoc comparisons (Duncan), the values of grade 0 differed from those of grades 1 and 2 for most parameters. When comparing symptoms (GOLD BD vs. AC, mMRC) and exacerbations (GOLD CD vs. AB), grade 0 was significantly different from grade 1 but not from grade 2. This indicates a similarity of symptom burden between grades 0 and 2.

The distribution of comorbidities is shown in Table 2, demonstrating that the prevalence of sleep apnea, hypertension, obesity, and diabetes significantly differed between the 3 grades. Regarding sleep apnea, grades 0 and

Table 2. Distribution of comorbidities according to GOLD grades 0, 1, and 2

Comorbidities	GOLD 0, *n* (%)	GOLD 1, *n* (%)	GOLD 2, *n* (%)
Asthma	91 (25.1)[&]	40 (19.4)	188 (19.5)
Bronchiectasis	12 (3.2)	7 (3.4)	29 (3.0)
Sleep apnea*	60 (16.0)[&]	27 (13.1)	102 (10.6)
Hypertension*	227 (62.7)[$,&]	105 (51.0)	541 (56.2)
Coronary heart disease	59 (16.3)	36 (17.5)	168 (17.5)
Myocardial infarction	25 (6.7)	13 (6.3)	84 (8.7)
Heart failure	28 (12.1)	8 (7.6)	45 (9.1)
Obesity (BMI >30 kg/m^2)**	149 (39.8)[$,&]	41 (19.9)	259 (27.0)
Diabetes**	77 (20.6)[$,&]	22 (10.7)	131 (13.6)
Hyperlipidemia	186 (51.4)[&]	105 (51.0)	436 (45.3)
Hyperuricemia	74 (20.4)	31 (15.0)	184 (19.1)
Osteoporosis	50 (13.8)	29 (14.1)	128 (13.3)
Gastrointestinal disorder	173 (47.8)	112 (54.4)	439 (45.6)
Mental disorder	109 (30.1)[&]	52 (25.2)	232 (24.1)
Peripheral polyneuropathy	34 (9.1)	16 (7.8)	65 (6.8)

Values given are numbers and percentages of the respective GOLD grade. The statistical comparisons were performed by χ^2 tests of contingency tables. * $p < 0.05$, different between groups. ** $p < 0.001$, different between groups. [$] $p < 0.01$, different from GOLD 1. [&] $p < 0.01$, different from GOLD 2 according to post hoc comparisons using the respective contingency subtables.

Table 3. The frequency of treatment with three major classes of respiratory medication

Medication	GOLD 0, *n* (%)	GOLD 1, *n* (%)	GOLD 2, *n* (%)
Only LABA	30 (8.0)	18 (8.7)	67 (7.0)
Only LAMA	31 (8.3)	21 (10.2)	80 (8.3)
Only LABA + LAMA**	27 (7.2)[&]	22 (10.7)	159 (16.5)
Only LABA + ICS**	83 (22.2)[&]	54 (26.2)	145 (15.1)
Triple therapy**	90 (24.1)[&]	41 (19.9)	393 (40.9)
Any LABA**	230 (61.5)[&]	135 (65.5)	764 (79.4%)
Any LAMA**	154 (41.2)[&]	88 (42.7)	645 (67.0)
Any ICS*	187 (50.0)[&]	104 (50.5)	555 (57.7)

Values given are numbers and percentages of the respective GOLD grade. The statistical comparisons were performed by χ^2 tests of contingency tables. Combination of drugs includes single and combined preparations. * $p < 0.05$, different between groups. ** $p < 0.001$, different between groups. [&] $p < 0.01$, different from GOLD 2 according to post hoc comparisons using the respective contingency subtables.

2 were different, regarding obesity grades 0 and 1 as well as grades 0 and 2, regarding hypertension grades 0 and 1 as well as grades 0 and 2, and regarding diabetes grades 0 and 1 as well as grades 0 and 2. Considering the results shown in Tables 1 and 2, patients of GOLD grade 0 showed higher BMI and a higher frequency of obesity associated with comorbidities such as hypertension, diabetes, and sleep apnea typically linked to obesity. The BMI did not change significantly over the 3 visits (repeated measures ANOVA, $p = 0.357$).

The frequency of treatment with 3 major classes of respiratory medication is shown in Table 3. The 3 grades differed from each other regarding the intake of any LABA, any LAMA, and any ICS, as well as dual and triple combinations of LABA, LAMA, and ICS. If there were differences, grade 0 was different from grade 2 but not grade 1.

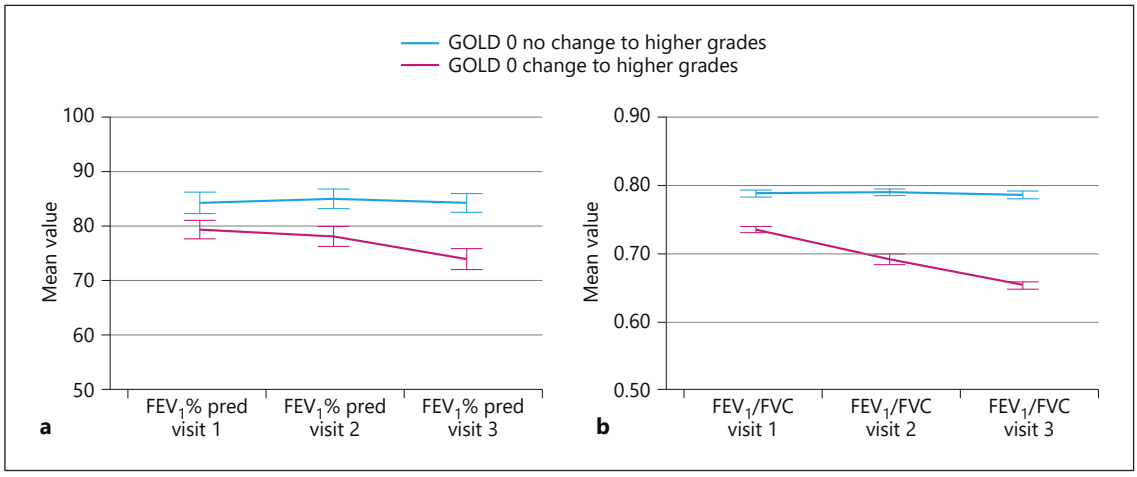

Fig. 1. a Course of lung function (FEV_1% predicted) for patients remaining in grade 0 over visits 1–3 and those changing to grade 1/2 without recurrence to grade 0. **b** Course of lung function (FEV_1/FVC) for patients remaining in grade 0 over visits 1–3 and those changing to grade 1/2 without recurrence to grade 0. FEV_1, forced expiratory volume; FVC, forced vital capacity.

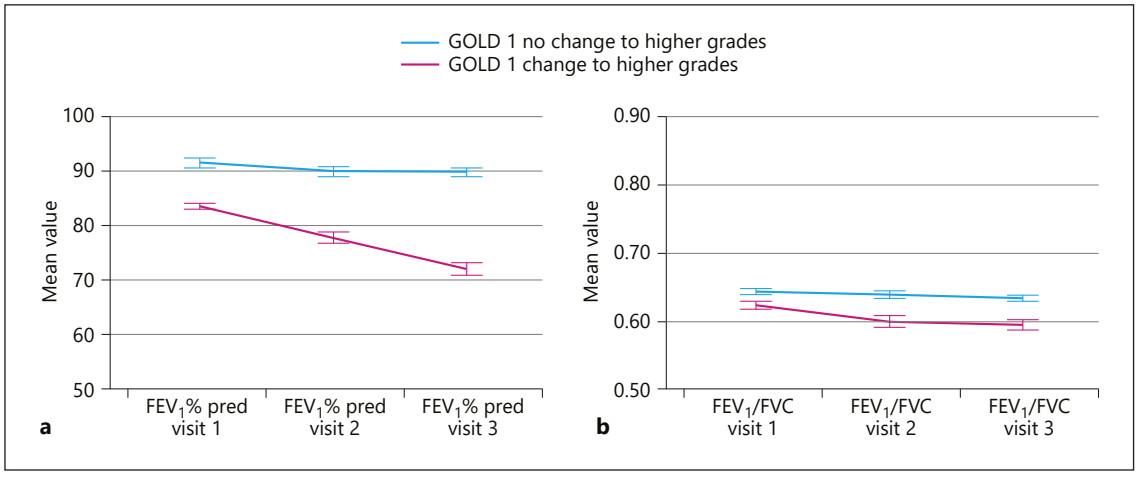

Fig. 2. a Course of lung function (FEV1% predicted) for patients remaining in grade 1 over visits 1–3 and those changing to grade 2/3 without recurrence to grade 1. **b** Course of lung function (FEV_1/FVC) for patients remaining in grade 1 over visits 1–3 and those changing to grade 2/3 without recurrence to grade 1. FEV_1, forced expiratory volume; FVC, forced vital capacity.

Changes in Grading over Time and Their Relationship to Functional Characteristics and Comorbidities

Among the 374 patients of grade 0 at visit 1, 107 remained in grade 0 at visits 2 and 3, whereas 58 patients changed their stage to grade 1 or 2 in these visits, without grade 0 reappearing, and 11 patients changed to grade 3 or 4. The remaining 112 GOLD 0 patients did not show a persistent change over the visits 2 and 3 and turned back to stage 0 in at least one visit. Among the 206 patients of grade 1 at visit 1, 80 remained in grade 1 at visits 2 and 3, whereas 51 patients changed to higher grades in these visits, without grade 1 reappearing, and 44 patients did not show a persistent change over the following visits, 2 and 3.

The course of lung function for patients remaining in grade 0 over visits 1–3 and those changing to grade 1 or 2 without recurrence to grade 0 is shown in Figure 1a and b for FEV_1% predicted and FEV_1/FVC, respectively. According to repeated measures analysis of variance for FEV_1/FVC, both the level and the slope of curves were

significantly different ($p < 0.001$, each). Similarly, the course of lung function for patients either remaining in grade 1 or changing to higher grades without returning to grade 1 in visits 1–3, is given in Figure 2. These figures suggest that in grade 0 the FEV_1/FVC was a better predictor of deterioration, while in grades 1/2 FEV_1 was better. Repeated measures analysis of FEV_1 also revealed a significant difference in level and slope between the 2 GOLD 1 groups.

In order to reveal which parameters were predictive for a change into a higher GOLD grade, multiple logistic regression analysis using age, BMI, sex, FEV_1% predicted, FEV_1/FVC% predicted, RV% predicted, TLC% predicted, ITGV% predicted, and TLCO% predicted as predictors was employed. For patients of initial grade 0, age, FEV_1/FVC% predicted and ITGV% predicted turned out to be relevant ($p < 0.05$ each). For patients of initial grade 1, only FEV_1% predicted was relevant ($p < 0.001$). This result underlines that FEV_1% predicted was of no predictive value in grade 0, in contrast to grade 1. Using the Youden index, a ROC analysis of FEV_1/FVC in GOLD 0 patients identified the value of 0.75 as the best cutoff value of FEV_1/FVC to discriminate between patients remaining stable over time versus those deteriorating. In both grades 0 and 1 at visit 1, the distribution of comorbidities did not significantly differ between patients remaining in visits 2 and 3 at the same grade and those increasing their grade.

Prediction of Mortality Risk in Grade 0 Patients

Associations of lung function with mortality of patients showing grade 0 at visit 1 were assessed over a follow-up of 3 years (until visit 4). In a previous investigation, a cutoff value of 80% predicted for FEV_1 was shown to be relevant for mortality risk in GOLD 0 patients [7]; we therefore specifically studied whether this cutoff value was also adequate in our study population. Indeed, besides age ($p < 0.05$), FEV_1% predicted was a relevant predictor ($p < 0.001$) of mortality. This was also true when FEV_1 was categorized according to values <80% predicted, as proposed in PRISm ($p = 0.038$), but even more when values <65% ($p = 0.001$) were chosen. The latter cutoff value showed a stronger association, with a hazard ratio of 13.7 compared to 9.0 for 80% predicted. The ratio FEV_1/FVC was not related to mortality in the grade 0 patients.

Sensitivity Analysis

To account for the variability in spirometric measurements, possibly arising from daily variations, we additionally defined a group of patients showing GOLD grade 0 at visits 1 and 2. Within this group, patients remaining in grade 0 at visit 3 were compared with those deteriorating into GOLD grade 1 or 2. It again turned out that a cutoff value of FEV_1/FVC of 0.75 was most predictive for the differentiation between the 2 groups, thereby confirming the result of the primary analyses. The result regarding the different roles of FEV_1 and FEV_1/FVC in GOLD groups 0 and 1 remained unchanged when excluding patients with asthma and bronchiectasis.

When repeating the survival analyses including the superdecliner patients changing into GOLD grades 3 and 4 at visits 2 and/or 3, there was still an association with FEV_1 being <65% predicted, although just not statistically significant ($p = 0.051$), whereas there was no relationship for a cutoff value of 80% predicted as proposed in PRISm ($p = 0.411$). This supports the adequacy of the 65% cutoff value.

Discussion

The present study elucidated the characteristics of COPD patients who did not match the established criterion of FEV_1/FVC < 0.7 according to GOLD [14] and were previously categorized as grade 0 [20]. This is a heterogeneous group of patients including those with an early stage of COPD potentially progressing, but also patients with no significant deterioration over time. The novel, robust finding was that patients with a ratio of FEV_1/FVC well above 0.7, that is, >0.75, were likely to remain in grade 0, whereas those with values lower than 0.75 were more likely to change into higher grades. Regarding mortality of GOLD grade 0 patients, the most relevant cutoff was that of FEV_1 being <65% predicted. These easily applicable criteria might be helpful for clinical evaluation in addition to other criteria referring to grade 0 patients [7].

In our study, patients of grade 0 showed a significant symptom burden which was more similar to that of grade 2 than that of grade 1 patients. The same was true for exacerbation history categorized according to GOLD (groups C/D vs. A/B). Lung function showed a heterogeneous pattern. In most parameters, grade 0 was more similar to grade 1, but in FVC, it was more similar to grade 2. The ratio FEV_1/FVC was much higher than in grade 1 or 2, and the same was true for CO diffusing capacity. This pattern suggested a combination of restrictive and obstructive lung disorder, in accordance with the finding of an elevated BMI and increased frequency of obesity [21]. Overall, the characteristics of grade 0 patients showed some similarities to those reported in previous studies

[22], but there were also differences, possibly related to differences in recruitment procedures.

Beyond the increased BMI, which did not change over the follow-up visits, other causes of restrictive lung function patterns are possible, such as interstitial lung diseases, but we did not have information to clarify this issue. The fact that KCO% predicted was not reduced but even elevated compared to grades 1 and 2 did not favor the assumption of interstitial lung disease, and there were also no changes in diffusing capacity over time. Attempts to define categories of GOLD 0 patients with distinctive patterns of symptoms, function, and comorbidities that were stable over time did not yield meaningful results, partially due to the low, statistically insufficient numbers of patients in such categories.

The usefulness of categorizations depends on their predictive value. We found that values of $FEV_1/FVC < 0.75$ were, on average, associated with a decrease in lung function over about 1.5 years that led to a recategorization into grade 1 or 2. Conversely, values >0.75 were, on average, associated with stability of grade 0 over time. Importantly, the grade 0 group moving to grades 1 and 2 showed lower FEV_1, with an average below 80% predicted, already at baseline, thereby satisfying the criterion for PRISm [7]. In patients with GOLD grade 1, FEV_1% predicted seemed more relevant than FEV_1/FVC for stability over time versus moving to higher grades. This suggests that both, FEV_1% predicted and FEV_1/FVC, have a predictive value, depending on the initial grade.

In line with previous studies [7], we also observed a link between mortality and lung function in grade 0 patients, but found a FEV_1 cutoff value of <65% predicted to be superior to that of 80% predicted, whereas FEV_1/FVC was not relevant. This suggests that in grade 0 patients, the optimal parameters and cutoff values are different for different outcomes. The findings also underlined the heterogeneity of these patients, which renders the comparison of studies difficult. For example, in the COPDGene cohort [22], grade 1 patients were more or less intermediate between grade 0 and 2–4 patients, whereas in our study they showed better values than both grade 0 and grade 2 patients, in some parameters. An interesting observation was that the disease burden seemed similar across grades as underlined by the fact that the amount of respiratory medication was also similar. This is further supported by a previous analysis, in which we found similar healthcare resource utilization and healthcare costs for patients with grades 0, 1, and 2 [23].

There has been a long controversy about the clinical usefulness of the former grade 0 categorization. The prediction that a patient of this grade is stable over time probably has implications regarding the intensity of monitoring and preventive measures. From our data, it appears that these patients can be recognized by values of lung function that are fairly above the FEV_1/FVC cutoff value of 0.7 proposed by GOLD. Patients of grade 0 have also been reported to be at risk regarding hospitalization and mortality [4], and the role of spirometric lung function for this has been evaluated in a number of studies, most recently by Bhatt et al. [24] and through an analysis in which patients with FEV_1% predicted <80 [7] (PRISm) were considered separately. Different from this study, we found a cutoff value of 65% predicted superior regarding the risk of mortality and we consider this value as more plausible regarding a relevant impairment. With FEV_1/FVC ratio being ≥0.7, 80% predicted of FEV_1 is probably not indicative of a major restrictive disorder and reduction in ventilator capacity, in contrast to 65% predicted.

The potential practical implications of our findings might be that patients with COPD-specific symptoms and FEV_1/FVC above 0.7 (a) should be screened for comorbidities in association with obesity, (b) have an elevated risk for lung function decline if their FEV_1/FVC is below 0.75, and (c) have an increased mortality risk if FEV_1 is below 65% predicted. These simple criteria might help in monitoring GOLD grade 0 patients, that is, suggesting lung function control every 6 months in case of FEV_1/FVC below 0.75.

Limitations

Despite the large sample size of COSYCONET, the number of patients fulfilling the criteria of GOLD 0 or PRISm was not large, thereby limiting the possibility for comparisons and categorizations. On the other hand, patients were extensively characterized and received follow-up visits over 1.5 years and a mortality follow-up of 3 years, although these follow-up times were only short. On the other hand, regarding therapeutic decisions, these follow-up times might be sufficient. All patients with a diagnosis of COPD were eligible for COSYCONET, but it might be that among patients with preserved ratio, those with more than average symptoms have been preferentially recruited; this could be relevant for the observation that in some measures grade 0 patients showed more similarity to grade 2 than to grade 1 patients. It might well be that in the absence of an obstructive lung function pattern but clinically suspected COPD, the physician assigns the diagnosis of COPD if symptoms are more severe. This, however, is a classification problem and does not affect the conclusion regarding the patients categorized as GOLD 0 in our study.

Conclusion

We found that COPD patients not matching the criterion of $FEV_1/FVC < 0.7$ and categorized previously as GOLD grade 0 showed high symptom burden, treatment intensity, and frequency of comorbidities on average but with large heterogeneity. Among these patients, those with $FEV_1/FVC > 0.75$ were likely to remain in grade 0 over time, whereas those with values between 0.70 and 0.75 were more likely to move to higher GOLD grades. Regarding mortality, the best predictor in the GOLD 0 patients was FEV_1 being <65% predicted, as indicator of a relevant restrictive lung function pattern partially associated with BMI. Our findings provide easily applicable criteria that might help in the clinical evaluation of patients with the diagnosis of COPD despite not fulfilling the established FEV_1/FVC criterion.

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Statement of Ethics

All assessments were approved by the central (Marburg [Ethikkommission FB Medizin Marburg]) and local (Bad Reichenhall [Ethikkommission bayerische Landesärztekammer]; Berlin [Ethikkommission Ärztekammer Berlin]; Bochum [Ethikkommission Medizinische Fakultät der RUB]; Borstel [Ethikkommission Universität Lübeck]; Coswig [Ethikkommission TU Dresden]; Donaustauf [Ethikkommission Universitätsklinikum Regensburg]; Essen [Ethikkommission Medizinische Fakultät Duisburg-Essen]; Gießen [Ethikkommission Fachbereich Medizin]; Greifswald [Ethikkommission Universitätsmedizin Greifswald]; Großhansdorf [Ethikkommission Ärztekammer Schleswig-Holstein]; Hamburg [Ethikkommission Ärztekammer Hamburg]; MHH Hannover/Coppenbrügge [MHH Ethikkommission]; Heidelberg Thorax/Uniklinik [Ethikkommission Universität Heidelberg]; Homburg [Ethikkommission Saarbrücken]; Immenhausen [Ethikkommission Landesärztekammer Hessen]; Kiel [Ethikkommission Christian-Albrechts-Universität zu Kiel]; Leipzig [Ethikkommission Universität Leipzig]; Löwenstein [Ethikkommission Landesärztekammer Baden-Württemberg]; Mainz [Ethikkommission Landesärztekammer Rheinland-Pfalz]; München LMU/Gauting [Ethikkommission Klinikum Universität München]; Nürnberg [Ethikkommission Friedrich-Alexander-Universität Erlangen Nürnberg]; Rostock [Ethikkommission Universität Rostock]; Berchtesgadener Land [Ethikkommission Land Salzburg]; Schmallenberg [Ethikkommission Ärztekammer Westfalen-Lippe]; Solingen [Ethikkommission Universität Witten-Herdecke]; Ulm [Ethikkommission Universität Ulm]; Würzburg [Ethikkommission Universität Würzburg]) Ethical Committees, and written informed consent was obtained from all patients to publish the data collected during the study period. The study was based on 2,741 patients recruited within the COSYCONET framework (ClinicalTrials.gov, Identifier: NCT01245933). For further information, refer to the following: Karch A., Vogelmeier C., Welte T., Bals R., Kauczor H.U., Biederer J., Heinrich J., Schulz H., Glaser S., Holle R. et al.: The German COPD cohort COSYCONET: aims, methods, and descriptive analysis of the study population at baseline. *Respir Med*. 2016;114:27–37.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest. Financial support provided to individuals is disclosed on the conflict of interest declaration provided from each single author.

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Author Contributions

Barbara Mayerhofer and Rudolf Jörres were involved in the conception of the study, analyzing and interpreting the data, statistical analysis, conceptualizing and drafting of the manuscript, approved the final submitted version, and agreed to be accountable for all aspects of the work. Johanna Lutter, Benjamin Waschki, Diego Kauffmann-Guerrero, Peter Alter, Franziska Trudzinski, Felix Herth, Rolf Holle, and Jürgen Behr were involved in the interpretation of the data from this analysis, took part in the discussion and critical revision of this manuscript, approved the final submitted version, and agreed to be accountable for all aspects of the work. Robert Bals and Henrik Watz were involved in the interpretation of the data from this analysis and drafting of the manuscript, approved the final submitted version, and agreed to be accountable for all aspects of the work. Tobias Welte and Claus Vogelmeier contributed to the overall design of COSYCONET, to the interpretation of the data from this analysis, and to the development and critical revision of the manuscript, approved the final submitted version, and agreed to be accountable for all aspects of the work. Kathrin Kahnert was involved in the conception of the study, statistical analysis and interpretation of the data, conceptualizing and drafting of the manuscript, approved the final submitted version, and agreed to be accountable for all aspects of the work.

Availability of Data and Material

The basic data are part of the German COPD cohort COSYCONET (www.asconet.net) and available upon request. There is a detailed procedure for this on the website of this network. Specifically, the data can be obtained by submission of a proposal that is evaluated by the steering committee. All results to which the manuscript refers to are documented appropriately in the text, figures, or tables.

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