**Clinical characteristics 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 FEV1/FVC ratio ≥0.7 are a heterogeneous group (former GOLD grade 0) with uncertainties regarding treatment and natural history. We investigated which lung function measures are predictive for deterioration in these patients.

**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 two visits or deteriorated persistently into grades 1 or 2. Their clinical characteristics were compared with those of GOLD 1 and 2 patients.

**Results**

Among 2741 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 FEV1/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 in GOLD 0, FEV1 %predicted and age were the relevant determinants, whereby a cut-off value of 65 % was superior to that of 80 % as proposed previously.

**Conclusion**

Regarding patients of the former GOLD grade 0, we identified simple criteria for FEV1/FVC and FEV1 %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 one second (FEV1) and forced vital capacity (FVC) being less than 0.7, the spirometric condition for COPD is met. These patients are then further categorized into grades 1 to 4 according to FEV1 %predicted [2]. There are, however, also patients with functional and clinical characteristics of COPD who do not fulfil the FEV1/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 to 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 FEV1/FVC≥0.7 were subcategorized according to FEV1. Patients with FEV1<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 to 4 grading are not rare in clinical practice and often treated with COPD medications [6]. Their actual categorisation 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 to 4 [6], using data of the COPD cohort COSYCONET. This cohort also comprises a considerable number of „uncategorized“, or „grade 0“, patients at the initial visit [9]. The present analysis addressed the question, 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 three visits covering 1.5 years follow-up time was analyzed. Moreover, baseline characteristics were compared to those of GOLD grade 1 or 2 patients.

**Methods**

**Study population**

COSYCONET is a multi-center 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 analysed [9]. Patients with initial GOLD grade 0 were identified based on their lung function showing FEV1/FVC ≥0.7 in the presence of symptoms of chronic bronchitis. All other patients were excluded. The study was approved by the respective ethical committees and all patients gave their written informed consent.

**Assessments**

All assessments were performed by the study protocol documented previously [9]. Lung function assessments included spirometry, bodyplethysmography 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 FEV1/FVC ≥0.7 were classified if their FEV1 %predicted was below 80% [7].

**Statistical analysis**

We used mean values and standard deviations for data descriptions. Comparison between groups were 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 super-decliners 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 two groups defined above were compared in the longitudinal and mortality analyses. An analogous approach was followed for patients showing grade 1 at visit 1. Logistic regression analyses were used to identify risk factors for deterioration of lung function over time, and Cox proportional Hazard regression analysis for the assessment of mortality and risk factors. Receiver operating characteristics (ROC analyses) and the Youden Index were used to identify optimal cut-off 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, 2741 patients were included [9], of whom 450 could not be categorized into GOLD stages 1 to 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 grades 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 three grades. According to post hoc comparisons (Duncan), the values of grade 0 differed from those of grade 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 three grades. Regarding sleep apnea, grades 0 and 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 table 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 three visits (repeated measures ANOVA, p=0.357).

The frequency of treatment with three major classes of respiratory medication is shown in table 3. The three grades differed from each other regarding the intake of any LABA, any LAMA, 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.

*Changes of grading over time and their relationship to functional characteristics, comorbidities and medication*

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 grades 1/2 in these visits, without grade 0 re-appearing, and 11 patients changed to grades 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 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 re-appearing, 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 to 3 and those changing to grades 1/2 without recurrence to grade 0 is shown in figure 1A and B for FEV1 %predicted and FEV1/FVC, respectively. 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 to 3, is given in figure 1. These figures suggest that in grade 0 the FEV1/FVC was a better predictor of deterioration, while in grades 1/2 FEV1 was better. In order to reveal which parameters were predictive for a change into a higher GOLD grade, multiple logistic regression analysis was employed. For patients of initial grade 0, age, FEV1/FVC %predicted and ITGV %predicted turned out to be relevant (p<0.05 each). For patients of initial grade 1, only FEV1 %predicted was relevant (p<0.001). This result underlines that FEV1 %predicted was of no predictive value in grade 0, in contrast to grade 1.

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.

*Predicion of mortality risk in grade 0 patients at visit 1*

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 cut-off value of 80% predicted for FEV1 was shown to be relevant for mortality risk in GOLD 0 patients [7], we therefore specifically studied wheter this cut-off value was also adequate in our population. Indeed, besides age (p< 0.05), FEV1 %predicted was a relevant predictor (p<0.001) of mortality. This was also true when FEV1 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 cut-off value showed a stronger association, with a Hazard Ratio of 13.7 compared to 9.0 for 80%predicted. The ratio FEV1/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 visit 1 and 2. Within this group, patients remaining in grade 0 at visit 3 were compared with those deteriorating into GOLD grades 1 or 2. It again turned out that a cut-off value of FEV1/FVC of 0.75 was most predictive for the differentiation between the two groups, thereby confirming the result of the primary analyses.

When repeating the survivial analyses excluding the super-decliner patients changing into GOLD grades 3 and 4 at visits 2 and/or 3, there was still an association with FEV1 being less than 65 %predicted, although just not statistically significant (p=0.051), whereas there was no relationship for a cut-off value of 80 %predicted as proposed in PRISm (p=0.411). This supports the adequacy of the 65% cut-off value.

**Discussion**

The present study elucidated the characteristics of COPD patients who did not match the established criterion of FEV1/FVC <0.7 according to GOLD [14] and were previously categeorized 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 FEV1/FVC >0.75, i.e. well above 0.7, were likely to remain in grade 0, whereas those with lower values than 0.75 were more likely to change into higher grades. Regarding mortality of GOLD grade 0 patients, the most relevant cut-off was that of FEV1 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 that 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 versus 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 FEV1/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 recruitement 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 favour 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 FEV1/FVC < 0.75 were, on average, associated with a decrease in lung function over about 1.5 years that led to a recategorization into grades 1 or 2. Conversely, values greater than 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 FEV1, with an average below 80 %predicted, already at baseline, thereby satiysfying the criterion for PRISm [7]. In patients with GOLD grade 1, FEV1 %predicted seemed more relevant than FEV1/FVC for stability over time versus moving to higher grades. This suggests that both, FEV1 %predicted and FEV1/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 FEV1 cut-off value <65 %predicted to be superior to that of 80 %predicted, whereas FEV1/FVC was not relevant. This suggests that in grade 0 patients the optimal parameters and cut-off values are different for different outcomes. The findings also underlined the heterogeniety 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 grade 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 FEV1/FVC cut-off 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 FEV1 %predicted <80 [7] (PRISm) were considered separately. Different from this study, we found a cut-off value of 65 %predicted superior regarding the risk of mortality, and we consider this value as more plausible regarding a relevant impairment. At a FEV1/FVC ratio being ≥0.7, 80 %predicted of FEV1 is probably not indicative of a major restrictive disorder and reduction in ventilatory capacity, in contrast to 65 %predicted.

The potential practical implications of our findings might be that patients with COPD-specific symptoms and FEV1/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 FEV1/FVC is below 0.75, and (c) have an increased mortality risk if FEV1 is below 65 %predicted. These simple criteria might help for the monitoring of GOLD grade 0 patients, i.e. suggesting lung function control every 6 months in case of FEV1/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. 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.

**Conclusion**

We found that COPD patients not matching the criterion of FEV1/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 FEV1/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 FEV1 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 FEV1/FVC criterion.

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