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CAT score single item analysis in patients with COPD: Results from COSYCONET

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ABSTRACT

The COPD Assessment Test (CAT) is in widespread use for the evaluation of patients with chronic obstructive pulmonary disease (COPD). We assessed whether the CAT items carry additional information beyond the sum score regarding COPD characteristics including emphysema.

Patients of GOLD grades 1 to 4 from the COPD cohort COSYCONET (German **CO**PD and **Sy**stemic Consequences - **Co**morbidities **Net**work) with complete CAT data were included (n = 2270), of whom 493 had chest CT evaluated for the presence of emphysema. Comorbidities and lung function were assessed following standardised procedures. Cross-sectional data analysis was based on multiple regression analysis of the single CAT items against a panel of comorbidities, lung function, or CT characteristics (qualitative score, 15th percentile of mean lung density), with age, BMI and gender as covariates. This was supported by exploratory factor analysis.

Regarding the relationship to comorbidities and emphysema, there were marked differences between CAT items, especially items 1 and 2 versus 3 to 8. This grouping was basically confirmed by factor analysis. Items 4 and 5, and to a lower degree 1, 2 and 6, appeared to be informative regarding the presence of emphysema, whereas the total score was not or less informative. Regarding comorbidities, similar findings as for the total CAT score were obtained for the modified Medical Research Council scale (mMRC) which was also informative regarding emphysema.

Our findings suggest that the usefulness of the CAT can be increased if evaluated on the basis of single items which may be indicating the presence of comorbidities and emphysema.

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1. Introduction

The COPD Assessment test (CAT) is a well-established tool for the characterisation of patients with COPD [1]. It comprises eight questions with an ordinal scale from 0 to 5 points for each item, resulting in a total score between 0 and 40. The commonly used cut-off value to distinguish less symptomatic from symptomatic patients is 10 [2,3]. Significant correlations between the CAT score and health status of COPD patients have been shown, including comorbidities [4,5], exacerbation risk [6] and lung function [7,8]. This is reflected in the CAT's role for the definition of GOLD groups A to D and recommendations for medication [2].

The CAT was developed using item response theory (IRT) [1], and items were only included if they met stringent statistical criteria showing that together they had reliable measurement properties to quantify the overall impact of COPD on health and wellbeing. However, COPD is a heterogeneous condition and whilst the CAT was designed to be 'agnostic' to the underlying pathology, its individual items may contain useful information reflecting different aspects of COPD. This has been explored in terms of using CAT items for COPD screening [9] but not for detailed analysis of COPD characteristics.

A standard tool to assess the homogeneity of a questionnaire is factor analysis, and a previous study found that the eight questions belonged to a single factor, i.e. represented one domain of the questionnaire [10], in concordance with its design via IRT and corresponding to a high value of Cronbach's alpha [1]. However, the first two questions addressing cough and sputum could measure a different dimension of COPD than the other six, which address dyspnoea, limitations of activity and self-confidence; such differences were already indicated in their use for COPD screening [9]. There seem to be few data in the literature on the relationship between single CAT items and clinical or functional characteristics of COPD. One study categorized respiratory versus non-respiratory symptoms in the evaluation of an intervention [11], another analysed the single items for the purpose of COPD screening [9], a further study identified different relationships between single items and comorbidities [12]. However, a comprehensive picture covering all major aspects of COPD including the presence of emphysema is missing until now. The objective of the present analysis was to perform such a comprehensive, detailed evaluation of the single CAT items in a large data set and to reveal, to which extent single CAT items, as opposed to the total score, carry additional information regarding COPD characteristics including comorbidities, lung function and emphysema.

2. Methods

2.1. Study population and assessments

The analysis was based on baseline data from COSYCONET (German COPD and Systemic Consequences – Comorbidities Network) patients with GOLD grades 1 to 4 and complete data regarding the CAT single items (n = 2270), including a subsample of 493 subjects with an available chest CT performed after enrolment into COSYCONET (termed as prospective chest CT), allowing for the assessment of emphysema. In addition, we used retrospective CT data for control purposes (sensitivity analysis) as derived from 309 patients using routine assessments prior to enrolment into the study [13,14]. The flow diagram (Fig. 1) illustrates the eligibility criteria, the selection of participants as well as the study size. The presence of emphysema was evaluated by a qualitative, binary emphysema score and the 15th percentile of mean lung density, as previously described [14]. The study protocol and assessments of COSYCONET have been described previously [13].

The definition of comorbidities was based on patients' reports of physician-based diagnoses. For some comorbidities, the intake of disease-specific medication was taken into account [15]; this applied to asthma, diabetes, hyperlipidemia, hyperuricemia, hypertension, osteoporosis and depression. The comorbidity "any cardiac history" was defined by the history of ischemic heart disease, myocardial infarction, or heart failure. Lung function testing followed established guidelines [16,17] that were implemented into the standard operating procedures of COSYCONET [13], while Global Lung Function Initiative (GLI) reference values were taken [18,19]. For the present analysis, we selected forced expiratory volume in 1 s (FEV1), the ratio of residual volume to total lung capacity (RV/TLC), and the transfer factor for carbon monoxide (TLCO). The CAT score (see Table S1a) was obtained following the recommended procedure. In parallel, dyspnoea was measured using the modified Medical Research Council (mMRC) (Table S1b) scale.

2.2. Statistical analysis

Mean values and standard deviations (SD), as well as 95% confidence intervals (CI) were computed for data description. Cronbach's alpha was computed to describe the internal consistency of the items. In principle, however, a high value of Cronbach's alpha does not exclude that different dimensions may be present within the data. Thus, exploratory factor analysis was used to explore this question, using the principle component method, Varimax rotation and a cut-off value of 1 for the

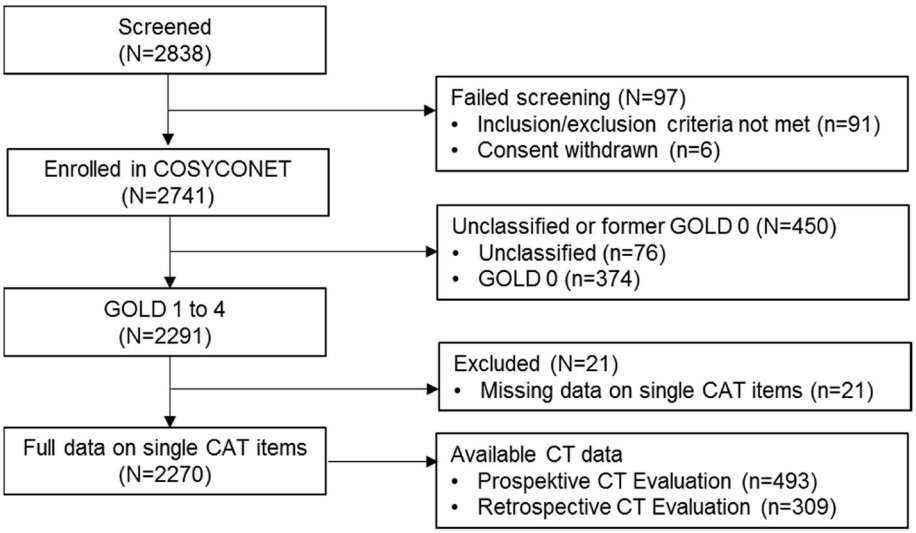


Fig. 1. Consort diagram comprising the selection of participants included in the analysis.

eigenvalues. The dependence of CAT items on comorbidities and lung function was determined by multiple linear regression analysis. In these analyses, comorbidities were binary, lung function parameters continuous variables, whereby either all comorbidities or all lung function variables were included. In case of CT variables, the analyses were performed with either the binary variable (emphysema score) or the continuous variable (15th percentile) but not both simultaneous due to their high correlation. In all regression analyses, gender, age and BMI were included as covariates. Sensitivity analysis using retrospective CT data was analysed accordingly. All analyses were performed using SPSS statistics 25 (IBM Corp., Armonk, NY, USA), and the level of statistical significance was assumed as $p < 0.05$.

3. Results

3.1. Baseline characteristics

The characteristics of the total study population and the subpopulation with prospective CT scans are given in Table 1. The group with CT had better lung function (spirometry and diffusing capacity) than those patients who did not have CT. The results for the single CAT items, the summary score and the mMRC are summarised in Fig. 2. Using the Mann-Whitney-U test, there were slight but significant ($p < 0.05$ each) differences between the groups of patients with and without prospective CT regarding items 2, 4, 5, 6 and 8, total CAT score and mMRC. In every case the scores in the CT groups were a little lower – as expected from lung function. Similar differences were observed when comparing the subgroup with retrospective CT scans with the complementary group.

Table 1
Patient characteristics of the total study population and the subpopulation with prospective CT scans.

Parameter	Total study cohort	Cohort without CT scans	Prospective CT cohort	p-value
gender m/f (%)	1384/886 (61/39)	1083/694 (61/39)	301/192 (61/39)	0.504
age	65.0 ± 8.4	65.52 ± 8.3	63.3 ± 8.5	<0.001
BMI	26.7 ± 5.2	26.7 ± 5.4	26.7 ± 5.8	0.383
smoking status (former or never smoker/ active smoker) (%)	1705/562 (75/25)	1337/437 (75/25)	368/125 (75/25)	0.392
packyears	49.2 ± 35.7	49.3 ± 35.9	48.6 ± 34.9	0.707
FEV_1 % predicted	52.5 ± 18.6	51.3 ± 18.4	56.8 ± 18.8	<0.001
RV/TLC	0.54 ± 0.11	0.55 ± 0.11	0.51 ± 0.10	<0.001
TLCO % predicted	56.2 ± 22.1	55.0 ± 22.3	60.5 ± 20.8	<0.001
GOLD groups A/B/C/D (mMRC based) (%)	873/574/296/526 (38/25/13/23)	640/465/226/445 (36/26/13/25)	233/109/70/81 (47/22/14/16)	<0.001
GOLD groups A/B/C/D (CAT based) (%)	243/1204/41/781 (11/53/2/34)	175/930/32/639 (10/52/2/36)	68/274/9/142 (14/56/2/29)	<0.001
GOLD grades 1–4 (%)	203/957/863/247 (9/42/38/11)	139/723/706/209 (8/41/40/12)	64/234/157/38 (13/48/32/8)	<0.001

The table shows mean values and standard deviations, as well as percentages. The p values refer to the comparison of the groups with vs without CT. For this purpose, unpaired t-tests and Chi-square statistics with contingency tables were used to compare the prospective CT cohort with the patients without CT scan. For abbreviations, see text. The GOLD categorizations are based either on FEV_1 (GOLD 1–4) or GOLD groups defined by symptoms and exacerbation risk (GOLD A-D) following the most recent GOLD recommendations [2]. Both the categorizations using CAT and mMRC are given.

3.2. Association with comorbidities, lung function and CT results

The relationship between CAT items and comorbidities is shown schematically in Table 2, illustrating the heterogeneous pattern of associations; for the corresponding numerical results see Table S2. The total CAT score and most of the single CAT items showed similar relationship to the comorbidities. These paralleled those observed with the mMRC score. In the subpopulation with CT scans, similar results were obtained, although fewer associations were significant.

In an analogous manner, associations with FEV1, RV/TLC and TLCO are given in Table 3, with numerical data in Table S3. In this case, the associations of the total CAT score and the mMRC were comparable to those of the single items. This table also presents the association with anthropometric data, which we omitted for the sake of brevity in the other tables.

Associations with CT emphysema characteristics are shown in Table 4, with numerical data in Table S4. The total CAT showed weaker associations with CT characteristics than items 4 and 5, which assess dyspnoea and physical activity limitations. The mMRC showed a similar association with the emphysema score and the 15th percentile.

For a sensitivity analysis we used retrospective CT scans ($n = 309$) that were obtained within 4 years prior to inclusion into COSYCONET [14]. These data showed essentially the same picture as the prospective data. In particular, items 4 and 5 were strongly associated with the emphysema score and the 15th percentile of mean lung density ($p < 0.001$ each), whereas the total CAT score was not significantly correlated, in contrast to mMRC. In this subgroup lung function was slightly worse than in the complementary group, although only FEV1 reached statistical significance (FEV1% predicted: 47 vs 53 ($p = 0.048$), RV/TLC: 0.57 vs. 0.54, TLCO% predicted: 49 vs. 57).

3.3. Factor analysis

The results of Tables 2–4 suggested that the CAT items measure different aspects of COPD. To reveal whether the items showed internal associations in parallel to their associations with COPD characteristics, we used factor analysis; this yielded two factors, the first comprising items 3 to 8, the second items 1 and 2, in both the total study population (Table 5) and the subpopulation with CT. The corresponding eigenvalues were 3.855 and 1.252, and 3.902 and 1.261, respectively, explaining 63.8% and 64.5% of variance. Despite this heterogeneity, the overall measure for consistency in terms of Cronbach's alpha showed high values, i.e. 0.844 for the total group and 0.848 for the CT group, in line with the fact that all CAT items were significantly correlated with each other.

4. Discussion

Our results obtained in a large group of patients with stable COPD indicate, that whilst the overall consistency of the CAT is confirmed, a factor analysis suggests that the items about cough and sputum may form a separate dimension from the remaining 6 items and that the single items of the CAT may contain additional information regarding comorbidities that is not captured so well in the total score. The pattern of associations with comorbidities resembled the separation into groups by factor analysis (see Tables 2–4). This is interesting, as this analysis concerned associations with COPD disease characteristics, the factor analysis, however, to the internal structure of the CAT questionnaire. This consistency lends support to the suggestion that the items 6–8 provide different information compared to items 1 and 2. In particular, items 4 and 5 are associated with the presence of emphysema diagnosed from CT scans, information that is lost or reduced when just the total score is considered. Taken together, our observations underline the usefulness of the CAT for characterizing COPD, but highlight that a single item or subgroup of items may carry additional information from that provided by the total score, especially in case of items 4 and 5.

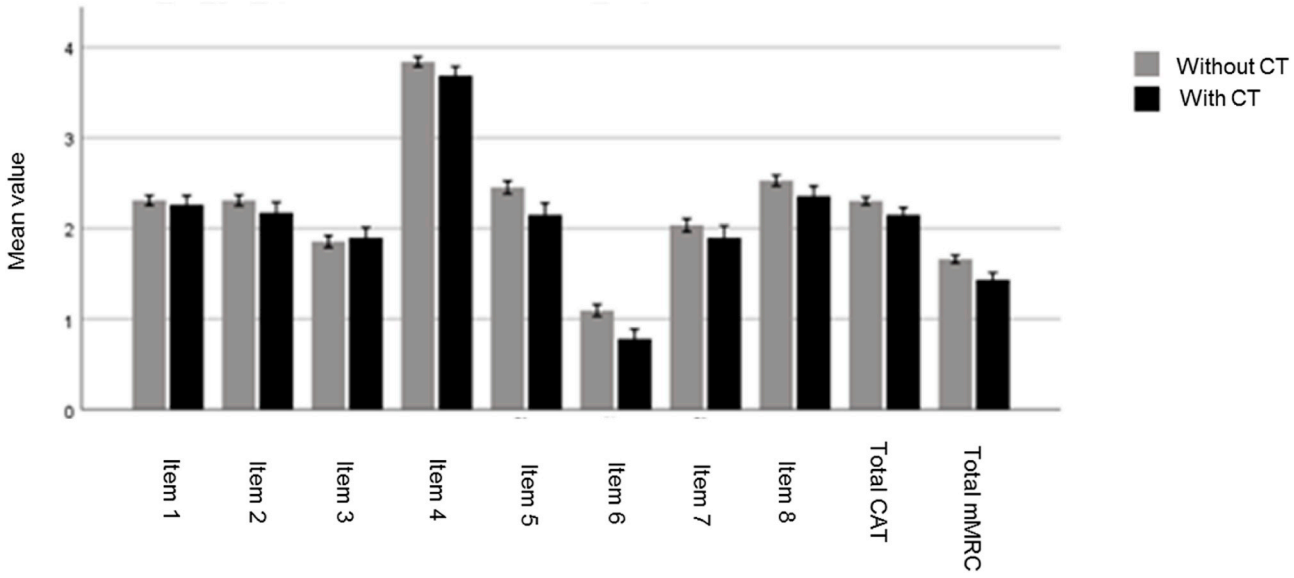


Fig. 2. Mean values of the single items of the CAT
The bars show mean values and 95% confidence intervals of the single CAT items, the total CAT score divided by 8 and the mMRC. Black bars give information on patients with CT scans, grey bars give information on patients without CT scans.

Table 2
Correlations between the single CAT items and a panel of comorbidities according to multiple regression analyses including age, gender and BMI as covariates (not shown, see Table 3) for the total population.

Comorbidity	item 1 "cough"	item 2 "phlegm"	item 3 "chest tightness"	item 4 "dyspnea"	item 5 "home acitivity"	item 6 "confidence leaving home"	item 7 "sleep disturbance"	item 8 "lack of energy"	total CAT score	total mMRC score
Asthma	p<0.05	p<0.001	p<0.001				p<0.001		p<0.01	
Sleep apnoea			p<0.05	p<0.01	p<0.01	p<0.01	p<0.001	p<0.05	p<0.001	p<0.01
Chronic bronchitis	p<0.001	p<0.001	p<0.001		p<0.01	p<0.001	p<0.001	p<0.01	p<0.001	p<0.01
Bronchiectasis	p<0.05	p<0.01								
Diabetes										p<0.05
Hyperlipidemia					p<0.05	p<0.01		p<0.05	p<0.05	p<0.001
Hyperuricemia		p<0.05								
Coronary artery disease										
Hypertension								p<0.01		
Any cardiac history					p<0.01	p<0.01		p<0.01	p<0.05	p<0.05
Osteoporosis			p<0.01	p<0.01	p<0.001	p<0.001	p<0.001	p<0.01	p<0.001	p<0.001
Gastroesophageal reflux							p<0.01			
Depression			p<0.05		p<0.001	p<0.001		p<0.001	p<0.001	p<0.01

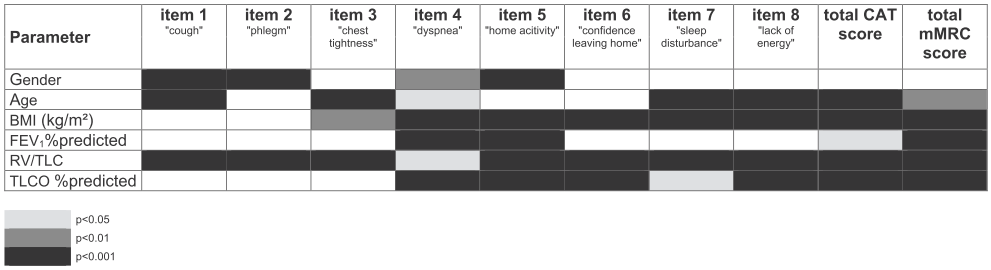
p<0.05
p<0.01
p<0.001

For the definition of comorbidities see methods. For the sake of clarity, the strength of associations according to their p-values is coded in three grades (light grey → $p < 0.05$; dark grey → $p < 0.01$; black → $p < 0.001$). The regression coefficients and 95% confidence intervals are given in the Supplemental Table S2.

Other investigators have also addressed the question whether the single CAT items carry specific information on specific COPD characteristics, such as comorbidities [12], phenotypes [20], or the distinction between respiratory and non-respiratory items [11]. The majority of studies, however, analysed only the total CAT score with regard to COPD characteristics [21,22]. The internal consistency of the CAT has been repeatedly demonstrated [21] and our results are in line with this, although the value of Cronbach's alpha was slightly lower than reported previously. Moreover, a factor analysis addressing the homogeneity of the items identified a single factor explaining about 62% of variance [10]. Irrespective of this, inspection of the CAT questions raises the suspicion that questions 1 and 2 might address different aspects than the other questions. Following this line of reasoning, we analysed the single CAT items with regard to comorbidities, lung function and emphysema. The presence of emphysema was determined by standardised CT scans that were performed in 493 patients within two years after inclusion into COSYCONET. Moreover, we had retrospective CT scans obtained for clinical purposes [14]. Although CT information was available only in subpopulations of patients, which showed slight differences in clinical characteristics compared to the remaining populations, the major findings regarding comorbidities and lung function were consistent with those of the total population. In addition, the prospective and retrospective CT data were congruent.

Regarding comorbidities, our study resembles that of Miyazaki and co-workers [12], who already provided a detailed analysis of the associations between single CAT items. The differences between the two studies might be explained by differences between populations, including the larger sample size in our analysis. This might explain why we found moderate associations of single questions e.g. with hyperlipidemia, which were absent in the study by Miyazaki et al. The

Table 3
Correlations between the single CAT items and lung function parameters according to multiple regression analyses including age, gender and BMI as covariates for the total population.



For abbreviations see methods. For the sake of clarity, the strength of associations according to their p-values is coded in three grades (light grey → $p < 0.05$; dark grey → $p < 0.01$; black → $p < 0.001$). The regression coefficients and 95% confidence intervals are given in the Supplemental Table S3.

Table 4
Correlations between the single CAT items and two CT-derived measures of lung emphysema according to logistic and linear multiple regression analyses including age, gender, BMI, packyears and smoking status as covariates (not shown) for the subpopulation with CT scans. The emphysema score was a binary, qualitative score, and the 15th percentile of mean lung density a continuous variable. For the sake of clarity, the strength of associations according to their p-values is coded in three grades (light grey → $p < 0.05$; dark grey → $p < 0.01$; black → $p < 0.001$). The regression coefficients and 95% confidence intervals are given in the Supplemental Table S4.

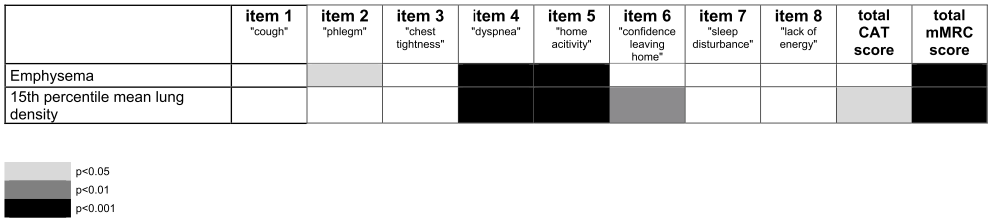


Table 5
Factor loadings of the single CAT items.

Rotated component matrix	Component 1	Component 2
Item 1	0.167	0.905
Item 2	0.198	0.892
Item 3	0.663	0.371
Item 4	0.704	0.127
Item 5	0.870	0.064
Item 6	0.706	0.127
Item 7	0.651	0.286
Item 8	0.759	0.182

Extraction method: Principle component analysis, Rotation method: Varimax with Kaiser-normalization

The table shows the factor loadings of the eight single CAT items onto the two factors identified, underlining the clear separation of items 1 and 2 versus items 3 to 8. The factor loadings represent the correlation coefficients of the respective item with the underlying hypothetical factor.

associations of items were different for osteoporosis, depression, asthma, chronic bronchitis and bronchiectasis. The heterogeneity was also apparent for the combined diagnosis of "any heart disease", hypertension and sleep apnoea. As a result, a previously proposed partition of CAT items as either respiratory (items 1 to 4) or non-respiratory [11], was not well reflected in our empirical results regarding the associations with comorbidities or the internal structure according to factor analysis. Our findings underline the assertion that the CAT is a powerful tool [22], the value of which might be even increased by looking at single items. Regarding comorbidities, the CAT sum score did not appear to behave markedly different from the mMRC score, which was also true for the associations with lung function.

We selected FEV1, RV/TLC and TLCO as measures of airway obstruction, lung hyperinflation and the capacity of gas uptake. Other lung function parameters were omitted due to the problems of collinearity, moreover we had found these parameters informative in previous COSYCONET analyses [23–25]. RV/TLC was related to all single items of the CAT as well as the sum score. TLCO, in contrast, was related to items 4 to 8, and FEV1 only to items 4 and 5. The lower number of associations with FEV1 was reflected in its weaker correlation with the sum score. Except for item 3, the pattern of relationships to lung function appeared to correspond to that observed in factor analysis.

An interesting finding was that the items related to FEV1 were also those strongest related to the CT findings, for both the qualitative emphysema score and the 15th percentile of mean lung density as a continuous measure of emphysema. This finding underscored the benefit of the single item analysis, since there were only weak or no significant relationships to the total CAT score. Previous studies reported weak to moderate correlations of the total CAT score with several indices of emphysema derived from CT scans [7,26]. Zhang et al. also analysed the mMRC and observed similar, and partially stronger, relationships of total mMRC with the CT indices for emphysema [26] compared to the findings in the present analysis. This fits well with our observation that the mMRC was related to both the qualitative diagnosis of emphysema and the 15th percentile of mean lung density, similar to the selected single CAT items. In any case, the relationship of single CAT items, especially 4 and 5, with the CT indices was stronger than that of the total score. One might even consider to define a subscore based on items 4 and 5 and to validate this within a meta-analysis of large COPD studies. This seems even more reasonable as one of the pathophysiological links between these two items and emphysema could be muscle wasting which is particularly present in emphysema.

When tentatively performing a receiver operator curve (ROC) analysis for items 4 and 5 regarding the presence of emphysema

(emphysema score), the areas under the curve (AUC) were 0.606 and 0.608, respectively, with optimal cut-off values of ≥ 4 and ≥ 2. As a clinical example, a patient with a score of at least 4 for item 4 and at least 2 for item 5 has a markedly increased risk for the presence of emphysema and therefore could be specifically screened by CT. CT-based emphysema screening is already recommended [27] but targeted screening of patients may reduce costs as well as radiation exposure. In view of the fact that the CAT is in widespread clinical use [21,22], it might be worthwhile to examine its single items before taking further steps in emphysema diagnostics.

4.1. Limitations

The present analysis was cross-sectional and therefore does not allow for causal inferences. At least, however, the analogy between the internal associations of CAT items and their associations with COPD characteristics supports the consistency of our findings. Regarding the CT evaluation, we restricted our analysis to the emphysema score and the 15th percentile of mean lung density as major parameters describing CT derived information regarding emphysema, for both the prospective and the retrospective data set [14]. The subpopulations of patients with CT showed some differences in their clinical characteristics compared to the patients without CT but most associations with lung function and comorbidities were reproduced in the subpopulations, and a possible lack of significance appeared to be mainly due to the differences in sample size. Information on comorbidities was derived from patients' reports of a doctor-based diagnosis, and wherever reasonable, the reports were supplemented by the evaluation of disease-specific medication [15]. This approach had turned out to be useful in previous analyses of COSYCONET data, including data on the association of comorbidities with GOLD groups A to D based on either CAT or mMRC [4]. The diagnosis of depression in the present analysis was based on the intake of specific medication, in accordance with a previous detailed analysis of the PHQ-9 screening tool [28], thereby avoiding difficulties in the diagnosis of this disorder.

5. Conclusion

Using data from the COPD cohort COSYCONET, we analysed the associations of the single items of the COPD Assessment Test (CAT) with a broad panel of COPD characteristics. It appeared that CAT items 1 to 2 referred to different characteristics compared to items 3 to 8. Moreover, CT-derived indices of lung emphysema were linked to items 4 and 5. These findings suggest that inspection of the single CAT items could help to identify clinical phenotypes of COPD by revealing information masked in the total score, which seems particularly true for the items 4 and 5 with regard to lung emphysema.

Ethics approval and consent to participate

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.

The study comprised 2270 patients recruited within the COSYCONET framework (ClinicalTrials.gov, Identifier: NCT01245933).

For further information see

Karch A, Vogelmeier C, Welte T, Bals R, Kauczor HU, 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.

Consent to publish

Within the ethical approval the participants of the study gave their consent to publish the data collected during the study period.

Availability of data and materials

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 which is evaluated by the steering committee. All results to which the manuscript refers to are documented by the appropriate in the text, figures or tables.

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The funding body had no involvement in the design of the study, or the collection, analysis or interpretation of the data.

Authors' contributions

Sarah Marietta von Siemens was 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.

Peter Alter was 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.

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Tobias Welte contributed to the overall design of COSYCONET, to the interpretation of the data from this analysis, 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.

Claus F. Vogelmeier contributed to the overall design of COSYCONET, to the interpretation of the data from this analysis, 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.

Rudolf A. Jörres was involved in the design and set-up of the study, as well as quality control, statistical analysis and conceptualizing and drafting 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 design and set-up of the study, as well as quality control, statistical analysis and conceptualizing and drafting of the manuscript, approved the final submitted version, and agreed to be accountable for all aspects of the work.

Declaration Competing interests

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2019.105810.

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