ELSEVIER
CrossMark
Journal of Clinical Epidemiology 67 (2014) 904−911
Journal of Clinical Epidemiology

Five comorbidities reflected the health status in patients with chronic obstructive pulmonary disease: the newly developed COMCOLD index ☆

Anja Frei[a,b,*], Patrick Muggensturm[c], Nirupama Putcha[d], Lara Siebeling[e], Marco Zoller[b], Cynthia M. Boyd[f], Gerben ter Riet[e], Milo A. Puhan[a,g]

[a]*Institute of Social and Preventive Medicine, Department of Epidemiology, University of Zurich, Hirschengraben 84, 8001 Zurich, Switzerland*
[b]*Institute of General Practice and Health Services Research, University of Zurich, Pestalozzistrasse 24, 8091 Zurich, Switzerland*
[c]*Horten Centre for Patient-Oriented Research, University of Zurich, Pestalozzistrasse 24, 8091 Zurich, Switzerland*
[d]*Division of Pulmonary & Critical Care Medicine, Department of Medicine, Johns Hopkins Hospital, 5501 Hopkins Bayview Circle JHAAC 4B.74, Baltimore, MD, 21224 USA*
[e]*Department of General Practice, Academic Medical Centre, University of Amsterdam, Meibergdreef 15, 1105 AZ, Amsterdam, The Netherlands*
[f]*Division of Geriatric Medicine and Gerontology, Department of Medicine, Johns Hopkins University School of Medicine, Center on Aging and Health 5200 Eastern Avenue Center Tower, 7th Floor, Mason F. Lord Building, Baltimore, MD, 21224 USA*
[g]*Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, 615 N. Wolfe St, Room E6153, Baltimore, MD, 21205 USA*

Accepted 12 March 2014; Published online 29 April 2014

Abstract

Objective: This study aimed to identify those comorbidities with greatest impact on patient-reported health status in patients with chronic obstructive pulmonary disease (COPD) and to develop a comorbidity index that reflects their combined impact.

Study Design and Setting: We included 408 Swiss and Dutch primary care patients with COPD from the International Collaborative Effort on Chronic Obstructive Lung Disease: Exacerbation Risk Index Cohorts (ICE COLD ERIC) in this cross-sectional analysis. Primary outcome was the Feeling Thermometer, a patient-reported health status instrument. We assessed the impact of comorbidities at five cohort assessment times using multiple linear regression adjusted for FEV1, retaining comorbidities with associations $P \leq 0.1$. We developed an index that reflects strength of association of comorbidities with health status.

Results: Depression (prevalence: 13.0%; regression coefficient: −9.00; 95% CI: −13.52, −4.48), anxiety (prevalence: 11.8%; regression coefficient: −5.53; 95% CI −10.25, −0.81), peripheral artery disease (prevalence: 6.4%; regression coefficient: −5.02; 95% CI−10.64, 0.60), cerebrovascular disease (prevalence: 8.8%; regression coefficient: −4.57; 95% CI −9.43, 0.29), and symptomatic heart disease (prevalence: 20.3%; regression coefficient: −3.81; 95% CI −7.23, −0.39) were most strongly associated with the Feeling Thermometer. These five comorbidities, weighted, compose the COMorbidities in Chronic Obstructive Lung Disease (COMCOLD) index.

Conclusion: The COMCOLD index reflects the combined impact of five important comorbidities from patients' perspective and complements existing comorbidity indices that predict death. It may help clinicians focus on comorbidities affecting patients' health status the most.

Keywords: Pulmonary disease; Chronic obstructive; Comorbidity; Health status; Patient-reported outcome; Health-related quality of life; Comorbidity index

1. Introduction

In patients with chronic obstructive pulmonary disease (COPD), comorbidities are highly prevalent. Prevalence of at least one comorbidity in COPD populations is often reported to be more than 50%, depending on the definition of a comorbidity (eg, inclusion of risk factors or focus on clinically manifest diseases), methodology of assessment (eg, patient or physician reported or assessed through additional tests), and the source population (eg, primary care patients, those hospitalized after acute exacerbation or population-based patient samples) [1−3]. There are several explanations for why comorbidities are so prevalent in patients with COPD, such as

Funding: This study is part of the prospective ICE COLD ERIC cohort study which was supported by the Swiss National Science Foundation (grant # 3233B0/115216/1), Dutch Asthma Foundation (grant # 3.4.07.045) and Zurich Lung League (unrestricted grant). Dr. C.M.B. was supported by the Paul Beeson Career Development Award Program (NIA 1K23AG032910, AFAR, The John A. Hartford Foundation, The Atlantic Philanthropies, The Starr Foundation and an anonymous donor).

Conflict of interest: The authors declare that they have no financial conflict of interests.

* Corresponding author. Tel.: +41-44-634-4360; fax: +41-44-634-4986.
E-mail address: Anja.Frei@ifspm.uzh.ch (A. Frei).

0895-4356/$ - see front matter
http://dx.doi.org/10.1016/j.jclinepi.2014.03.005

What is new?

Key findings

- Among common comorbidities, depression, anxiety, peripheral artery disease, cerebrovascular disease, and symptomatic heart disease have the largest impact on patient-reported health status in patients with chronic obstructive pulmonary disease (COPD) independent of FEV1.
- This combination of comorbidities is different from comorbidities included in existing comorbidity indices like the Charlson index that predict mortality. This suggests that the outcome of interest should be defined carefully when selecting a specific comorbidity index.

What this adds to what is known?

- Although there are several comorbidity indices available for patients with COPD that were developed to predict mortality, no comorbidity index exists that quantifies the combined impact of comorbidities on patient-reported health status.

What is the implication, what should change now?

- Researchers and clinicians should carefully consider the outcome an index predicts.
- The COMorbidities in Chronic Obstructive Lung Disease index presented here may help clinicians to focus on comorbidities with greatest impact from the patients' perspective, and complements existing comorbidity indices predicting death. Researchers may use the index to efficiently adjust for confounding by comorbidities or to assess modification of effects of COPD treatments.

older age, physical inactivity or shared risk factors (eg, smoking or systemic inflammation) [4].

Attempts have been made to measure the relevance of multi-morbidity. Metrics for multi-morbidity include simple counts (ie, the sum of separate comorbidities) or indices where the relative severity of different comorbidities is considered [5,6]. Examples include the Charlson index [7], the Cumulative Illness Rating Scale [8], the Index of Coexisting Disease [9], and the Kaplan index [10]. These indices are, however, of limited use for patients with COPD because they were developed in mixed patient populations [8] or index diseases other than COPD [7,9,10]. Furthermore, for commonly used indices, often only mortality was considered to weigh the relative severity of the diseases [7]. Mortality was also the outcome of the recently developed COPD specific comorbidity test (COTE index), which identified 12 comorbidities that predicted mortality in patients with COPD [11].

Like mortality, patient-reported health status and health-related quality of life (HRQL) are important measures for patients with COPD, which are frequently used as outcomes in clinical research. We use health status as a patient-reported global measure to express the impact of physical and mental morbidity on self-perceived health. There are data to suggest that health status and HRQL are related but distinct constructs [12]. Although some studies looked at the impact of single or multiple comorbidities on HRQL [13–17], to our knowledge no comorbidity index exists that quantifies the combined impact of comorbidities on HRQL or patient-reported health status. Such an index could inform clinicians about comorbidities that deserve particular attention to increase quality of treatment. Researchers could use an index summarizing the impact of comorbidities to assess their combined impact on treatment effects, in particular if health status or HRQL is the outcome. The aim of this study was to identify those comorbidities with the greatest impact on patient-reported health status in patients with COPD and to develop a COPD comorbidity index, the COMorbidities in Chronic Obstructive Lung Disease (COMCOLD) index that reflects their combined impact and that enables researchers and clinicians to discriminate between patients.

2. Methods

2.1. Study design

We conducted a cross-sectional analysis nested within the prospective the International Collaborative Effort on Chronic Obstructive Lung Disease: Exacerbation Risk Index Cohorts (ICE COLD ERIC) cohorts. ICE COLD ERIC is an international multi-site prospective cohort study with primary care patients with COPD from Switzerland and the Netherlands. All included patients have provided written informed consent. The study has been approved of by all local ethics committees and is registered on www.ClinicalTrials.gov (NCT00706602). Detailed information on the study design [18] and the baseline results [19] were published elsewhere.

2.2. Study population

All patients included in the ICE COLD ERIC cohort were eligible for this analysis. All patients were $\geq$40 years of age, had Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages 2 to 4 and were free of exacerbation for at least 4 weeks at baseline. Exclusion criteria were an expected life expectancy of $\leq$12 months (assessed by physician), dementia, psychosis, or other psychiatric morbidity that would invalidate assessment of patient-reported parameters and inability to complete the baseline assessment due to language difficulties.

Patients were enrolled between April 2008 and August 2009 (baseline assessment) [18], and follow-up assessments took place every 6 months. If not stated otherwise, the analyses are based on the baseline assessment data.

2.3. Primary outcome for patient-reported health status

The Feeling Thermometer (FT), a patient-reported health status instrument, was the primary outcome. The FT is a modified visual analogue scale presented in the form of a thermometer with 100 marked intervals (0 = dead, 100 = perfect health) that has been validated in patients with COPD [20,21]. The FT is also part of the extensively used and validated EQ-5D developed by the EuroQol group [22]. We chose the FT as the primary outcome to use a generic health status instrument to capture the potential influence of any comorbidity on health status as opposed to a COPD-specific HRQL instrument like the Chronic Respiratory Questionnaire (CRQ) [23] that is likely to be insensitive to effects of some comorbidities.

2.4. Ascertainment and classification of comorbidities

The assessment of the comorbidities was done by experienced and well-trained study nurses or physicians during the baseline visits of the cohort study, which took place at the primary care practices. The patients were asked which comorbidities they had using open-ended questions. The patients also brought a list with all drugs they were taking to the baseline interview. The study nurses or physicians compared the patient-reported comorbidities with the list of medications (and in Switzerland also with the patient records) and clarified with the general practitioners any uncertainties or mismatches between the patients' reports, the drug list, or the patients' obvious heath condition. We defined comorbidities based on criteria used in prior literature [24,25]. Obesity was defined as body mass index (BMI) $\geq$30 kg/m^2, serum creatinine measurements were used to calculate glomerular filtration rates (GFRs), and chronic kidney disease was defined by self-report as well as GFR of $<$60 mL/min using an accepted equation [26]. Diagnoses of coronary heart disease and heart failure were considered as symptomatic heart disease, and diagnoses cerebrovascular accident and transient ischemic attack as cerebrovascular disease. To identify patients with anxiety and depression, we also used the scores from the Hospital Anxiety and Depression Scale [27] and defined patients as having anxiety or depression if their score was 11 points or higher [28].

2.5. A priori criteria of the COMCOLD index

We defined the following a priori criteria for the COMCOLD index: (1) we did not consider asthma as a comorbidity because the symptoms can be very similar to those of COPD; (2) the higher the index the greater the impact of comorbidities on health status of patients with COPD, independent from COPD severity; (3) the index should be interpretable in terms of its impact on patient-reported health status. Therefore, we determined that each point increase should relate to the minimal important difference (MID) of the FT (6 points) [21].

2.6. Statistical analysis and development of the COMCOLD index

Continuous variables are presented as means with standard deviations (SDs), categorical data as frequencies and percentages. We examined the prevalence of existing comorbidities and only considered those with a prevalence $>$5% in the development of the index. We reported data on the prevalence of rarer, miscellaneous comorbidities categorized by disease group. To determine the independent impact of comorbidities on patient-reported health status, we used regression models to calculate associations between each comorbidity (with prevalence $>$5%) or categorized disease groups (including comorbidities with prevalence $\leq$5%) and health status (FT) as outcome individually, adjusted for FEV1 in % predicted.

To decide on inclusion of comorbidities that reflect the combined impact on health status (FT) for the index, we applied two selection procedures: (1) stepwise backward selection of comorbidities by regression analysis and (2) consistency over time by repeating the analyses for five cohort assessment times. In detail, we conducted a multiple linear regression model with the FT as dependent variable and comorbidities with prevalence $>$5% as independent variables with backward selection and a $P \leq 0.1$ criterion to retain variables in the model, adjusted for FEV1 in % predicted. We performed this model with the data of the baseline assessment and repeated it with the data of the 6, 12, 18, and 24 months follow-up assessments. We did not adjust for age and sex because such adjustment could mask the effect of comorbidities on health status. However, we conducted a sensitivity analysis where we additionally adjusted for age and sex. We conducted the final multiple linear regression analysis on which the index is based on the data of the baseline assessment, the most comprehensive sample where no patients are lost to follow-up. For the final regression model, we selected those comorbidities, which were retained in the backward selection model (adjusted for FEV1 in % predicted) at least three assessment times of the five.

We developed the COMCOLD index by transforming the final model's regression coefficients into an index system that reflected the underlying association of the included comorbidities with health status (1 point per increase of the coefficient by 0.25 MID, 1.5 points of the FT). We tested for possible interaction between FEV1 in % predicted and the index. To assess construct validity, we calculated Pearson correlation coefficients between the COMCOLD index and the following validation measures: (1) The total number of drugs taken regularly as another measure of

Table 1. Patient characteristics of the COPD patients enrolled in the cohort study (n = 408)

Characteristics	Mean (SD) or n (%)[a]
Age	67.3 (10.0)
Sex (male, n, %)	233 (57.1)
FEV1 in % predicted	55.6 (16.6)
MRC	1.9 (1.5)
Feeling thermometer	68.3 (15.5)
Number of comorbidities	3.2 (2.2)
Number of drugs	2.9 (2.3)
GOLD stage	II: 261 (64.0); III: 89 (21.8); IV: 58 (14.2)
New GOLD stage	A: 171 (41.9); B: 90 (22.1); C: 55 (13.5); D: 92 (22.6)

Abbreviations: FT, Feeling Thermometer; GOLD, Global Initiative for Chronic Obstructive Lung Disease; MRC, Medical Research Council questionnaire; SD, standard deviation.

[a] One patient did not complete the FT.

multi-morbidity (moderate positive correlations expected), (2) exercise capacity assessed by sit-to-stand test [29] (moderate negative correlations expected), (3) physical activity assessed by self-administered Longitudinal Aging Study Amsterdam (LASA) Physical Activity Questionnaire [30] (moderate negative correlations expected), and (4) disease-specific HRQL assessed by CRQ [23] [moderate negative correlations with CRQ domains expected and correlations for the more generic domains (emotional and fatigue) expected to be stronger than those for the more COPD-specific domains (dyspnea and mastery)]. All analyses were done using STATA (version 11.2, 12, and 13; StataCorp LP, College Station, TX, USA).

3. Results

3.1. Patient characteristics and comorbidities

We excluded one patient who did not complete the FT at baseline but included all other 408 patients in the analysis. A total of 57.1% of the patients were male, and the mean age was 67.3 years (SD = 10.0) (Table 1). A total of 90.7% (n = 370) of the patients had at least one comorbidity: 16.9% (n = 69) had one, 17.4% (n = 71) had two, 17.7% (n = 72) had three, and 38.7% (n = 158) had ≥4 comorbidities. The most prevalent comorbidities were hypertension (42.2%), followed by arthrosis (29.4%), obesity (20.3%), and symptomatic heart disease (coronary heart disease or heart failure, 20.3%) (Fig. 1).

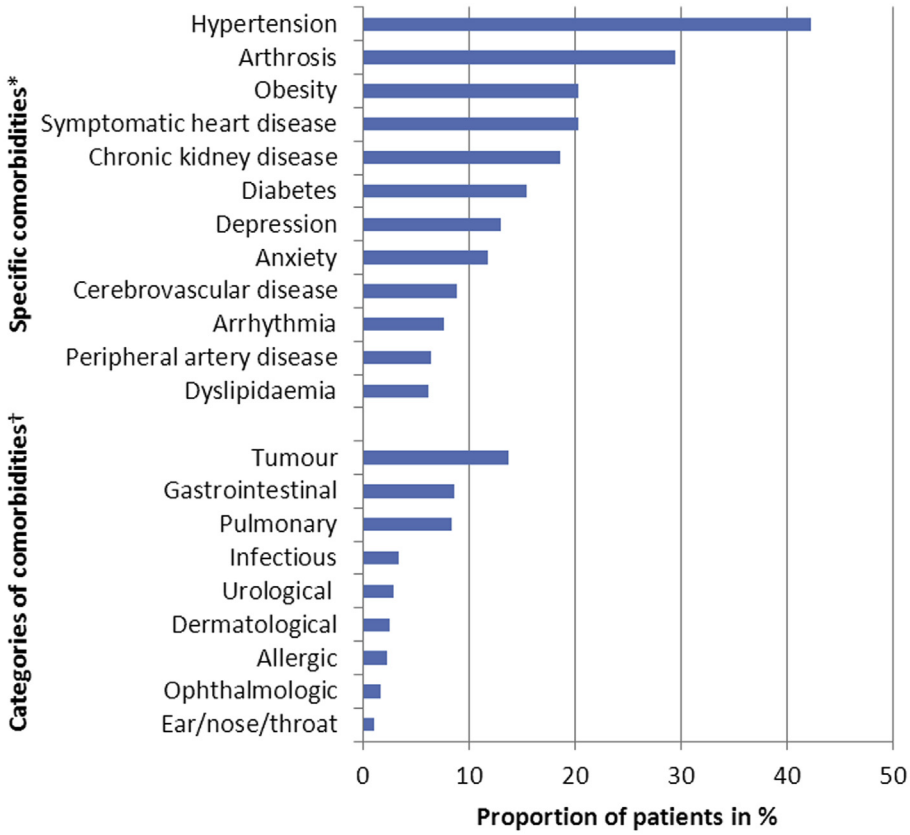

Fig. 1. Prevalence of specific comorbidities (prevalence > 5%) and categories of comorbidities (categorized specific comorbidities with prevalence ≤5%) (n = 408).

Table 2. Individual associations of specific comorbidities (prevalence >5%) and disease groups (categorized specific comorbidities with prevalence ≤5%) with patient-reported health status (FT) (n = 408)

Specific comorbidities and disease groups	Coefficients[a,b] (change in FT score if comorbidity is present)	95% CI
Specific comorbidities with prevalence >5%		
Hypertension	−3.21	−6.12, −0.3
Arthrosis	−1.96	−5.12, 1.20
Obesity (BMI ≥30)	−6.36	−9.91, −2.81
Symptomatic heart disease[c]	−4.44	−8.00, −0.88
Chronic kidney disease	−2.35	−6.05, 1.35
Diabetes	−5.50	−9.46, −1.55
Depression	−11.42	−15.57, −7.27
Anxiety	−9.29	−13.69, −4.89
Cerebrovascular disease[d]	−4.04	−9.12, 1.03
Arrhythmia	1.83	−3.61, 7.27
Peripheral artery disease	−5.15	−11.04, 0.73
Dyslipidemia	−3.93	−9.94, 2.08
Disease groups, containing categorized specific comorbidities with prevalence ≤5%		
Tumor disease group	0.95	−3.24, 5.14
Gastrointestinal disease group	0.59	−4.60, 5.78
Pulmonary disease group	−0.87	−6.09, 4.34
Infectious disease group	−8.50	−16.38, −0.62
Urological disease group	−4.80	−13.37, 3.78
Dermatological disease group	0.91	−8.44, 10.26
Allergic disease group	−4.19	−14.00, 5.63
Ophthalmologic disease group	7.66	−3.43, 18.74
Ear, nose, throat disease group	7.95	−6.67, 22.57

Abbreviations: CI, confidence interval; FT, Feeling Thermometer.
[a] All adjusted for FEV1 in % predicted.
[b] The coefficients describe the change in health status in points on the FT.
[c] Coronary heart disease and/or heart failure.
[d] Cerebrovascular accident or transient ischemic attack.

3.2. Impact of comorbidities on patient-reported health status

Adjusted for FEV1 in % predicted, depression, anxiety, obesity, diabetes, symptomatic heart disease, hypertension, and peripheral artery disease were individually associated (regression coefficients of ≥3 = at least 0.5 MID of FT; $P \leq 0.1$) with FT scores (Table 2).

Table 3. Final regression model with selected specific comorbidities as predictors and patient-reported health status (FT) as outcome (n = 408)[a]

Comorbidity	Coefficients	95% CI
Depression	−9.00	−13.52, −4.48
Anxiety	−5.53	−10.25, −0.81
Peripheral artery disease	−5.02	−10.64, 0.60
Cerebrovascular disease[b]	−4.57	−9.43, 0.29
Symptomatic heart disease[c]	−3.81	−7.23, −0.39

Abbreviation: FT, Feeling Thermometer.
[a] Based on baseline assessment data and adjusted for FEV1 in % predicted.
[b] Cerebrovascular accident or transient ischemic attack.
[c] Coronary heart disease and/or heart failure.

Table 4. COMCOLD index (range 0–19)

Comorbidity	Points
Depression	6
Anxiety	4
Peripheral artery disease	3
Cerebrovascular disease[a]	3
Symptomatic heart disease[b]	3

Abbreviation: COMCOLD, COMorbidities in Chronic Obstructive Lung Disease.
[a] Cerebrovascular accident or transient ischemic attack.
[b] Coronary heart disease and/or heart failure.

Depression, anxiety, cerebrovascular disease (cerebrovascular accident or transient ischemic attack), peripheral artery disease, and symptomatic heart disease remained at least at three of five assessment times in the multiple backward selection regression model and, therefore, were considered for the final regression analysis. Hypertension, arthrosis, diabetes, and dyslipidemia were removed from the model at all five assessments, whereas obesity, chronic kidney disease, and arrhythmia each remained in a model once. Table 3 shows the results of the final regression analysis. The sensitivity analysis that also adjusted for age and sex resulted in almost identical coefficients for comorbidities.

3.3. Development of the COMCOLD index

We generated the index that reflects the strength of association between each of the five comorbidities with health status: 6 points for depression (coefficient, −9.00), 4 points for anxiety (coefficient, −5.53), and 3 points for peripheral artery disease (coefficient, −5.02), cerebrovascular disease (coefficient, −4.57) and symptomatic heart disease (coefficient, −3.81). This resulted in an index ranging from 0 (no impact of comorbidity on health status) to 19 (very large impact of comorbidity on health status) (Table 4). We found no interaction between FEV1 in % predicted and the index (P = 0.87). Correlations of the COMCOLD index with validation measures were in the ranges we had expected (Table 5).

Table 5. Construct validity: Pearson correlation coefficient between COMCOLD index and other measures (n = 408)

Measures	Pearson's correlation coefficients (95% CI)
Drug count	0.36 (0.27, 0.44)
Sit-to-stand test[a]	−0.20 (−0.30, −0.10)
LAPAQ score	−0.30 (−0.39, −0.21)
CRQ dyspnea	−0.25 (−0.34, −0.16)
CRQ fatigue	−0.38 (−0.46, −0.30)
CRQ emotional	−0.49 (−0.56, −0.41)
CRQ mastery	−0.35 (−0.43, −0.26)

Abbreviations: CI, confidence interval; COMCOLD, COMorbidities in Chronic Obstructive Lung Disease; CRQ, Chronic Respiratory Questionnaire; LAPAQ, LASA Physical Activity Questionnaire.
[a] n = 373.

4. Discussion

Our study showed that depression had the largest impact on patient-reported health status of patients with COPD, followed by anxiety, peripheral artery disease, cerebrovascular disease, and symptomatic heart disease. The COMCOLD index reflects the impact of these five comorbidities on health status in patients with COPD and may be attractive for both clinicians and researchers.

Overall, our results illustrate that researchers and clinicians should carefully consider the outcome an index predicts. Comorbidity indices developed to predict mortality are not designed to predict a patient-reported health outcome where other comorbidities are likely to be relevant. One apparent difference between the COMCOLD index and comorbidity indices that were developed to predict mortality, like the Charlson index [7] or the recently presented COPD-specific COTE index [11], is the role of mental diseases. Depression was most strongly associated with poor health status and contributed more than any other comorbidity to the COMCOLD index. Depression is neither part of the Charlson index nor of the COTE index.

Interestingly, anxiety, the other psychiatric disease that was strongly and independently associated with health status in our study, was also found to be associated with mortality in women and contributes to the COTE index [11]. The relevance of psychiatric comorbidities was also shown in a recently presented comorbidity index that was developed based on how well diagnoses were associated with generic HRQL in patients with any chronic condition, not specifically in patients with COPD. Anxiety and depression not only had the greatest association with the Short Form-12 mental component summary score, but were also related to the Short Form-12 physical component summary score [31].

We further found cerebrovascular disease and peripheral artery disease to be meaningfully associated with worse health status. Cerebrovascular disease and peripheral artery disease also contribute to the Charlson index but were not related to mortality risk in the study by Divo et al. [11]. In contrast, symptomatic heart disease is both relevant for patient-reported health status and mortality. Not surprisingly, cancer diagnoses contribute most to indices predicting death [7,11]. In our study, the combined category ‘‘any tumor disease’’ was not found to be associated with patient-reported health status, and we did not assess individual cancers due to low prevalence of specific cancers ($<5\%$). One possible explanation for the missing impact could be that we excluded patients with life expectancy with less than 12 months [18].

Previous studies assessing associations between comorbidities and patient-reported health outcomes in patients with COPD usually focused on HRQL, not particularly on health status. Consistently, prior studies have found associations between an increasing number of comorbidities and decreasing HRQL in patients with COPD, but the contribution of specific comorbidities was less clear [2,16,17]. Among the five relevant comorbidities detected in our study, depression and anxiety were previously found to be associated with impaired HRQL in a study that assessed the impact of these two disorders only [13]. Crisafulli et al. [32] found that heart disease significantly reduced the beneficial effects of pulmonary rehabilitation on perceived disease-specific HRQL in patients with COPD. In contrast to our results, Wijnhoven et al. [17] found that out of three interviewer-assessed chronic comorbidities (hypertension, cardiac diseases, and musculoskeletal disorders), only musculoskeletal disorders were associated with poor generic HRQL in patients with COPD. Van Manen et al. [15] found that COPD and comorbidity were related to impairment in the SF-36 dimensions of physical functioning, vitality, and general health. Impairment in the SF-36 dimensions of social and emotional functioning did not seem to be primarily related to COPD, but rather to the presence of comorbidities. Besides, Lopez Varela et al. [2] found in a population-based study on COPD prevalence that out of seven selected self-reported comorbidities, diabetes was the comorbidity that most affected the general health status of individuals with COPD in bivariate analysis. Diabetes was also found to have an independent impact on health status in our study; however, it lost its impact when considered together with other comorbidities in multiple regression analysis.

A limitation of our study is that we focused on comorbidities that had at least a prevalence of 5% or more in our cohort. Although the impact of rarer comorbidities is likely to be smaller from a population perspective, they may still represent a substantial burden in terms of effect on health status for individual patients. However, we decided not to consider them because fewer cases lead to lower precision for the estimates of associations. Another limitation is that the COMCOLD index does not consider that for some disease combinations, a synergistic effect on health status may exist. However, a recently published community-based cohort study found that effects of interaction between comorbidities in elderly on several health outcomes including self-rated health were primarily additive, not synergistic [33]. Finally, further research is needed to examine whether the index can be replicated in other populations of patients with COPD.

Strength of our study is the comprehensive assessment of the data on comorbidities based on several sources that included patient reports, patient charts (ie, physicians reports; Switzerland only) and additional tests (eg, serum creatinine). Because we were able to verify some of the comorbidity data of patients with the additional tests after publication of the baseline results [19], descriptive comorbidity results from our cohort have slightly changed. Furthermore, the population from primary care settings in two countries enabled us to assess the full spectrum of COPD and comorbidities, which increased the chance of

finding associations that are broadly applicable. Additionally, with the FT, we used a well-validated and easy-to-use instrument that assesses the patients' generic health status. Because a disease-specific quality of life instrument like for example the CRQ or the St. George's Respiratory Questionnaire focuses on COPD-specific physical (eg, dyspnea, fatigue) and mental impairment (eg, depression, anxiety), it is likely to miss the impact of some comorbidities.

In practice, the COMCOLD index can help clinicians to identify burden from comorbidities in patients with COPD. A high COMCOLD score reflects a substantial level of burden for the patient. This overall impression can be useful to discuss and prioritize treatment options with the patient and prevent overtreatment. Overtreatment will most likely be an issue in this older, multi-morbid patient population, for whom clinical practice guidelines from several diseases must be integrated to propose carefully individualized treatment [34], if possible at all. In addition, the COMCOLD index supports clinicians to recognize comorbidities and treatment possibilities that are not known to be associated with an increased risk of death in patients with COPD but rather influence how patients are currently feeling. For example, a patient with COPD with comorbid depression and peripheral artery disease is not at much higher risk for death according to the Charlson index (1 point of 37 possible points) or COTE index (0 points of 19 or 25 possible points). However, the COMCOLD index (9 points of 19 possible points) indicates that this patient suffers from a decreased health status and may benefit from effective treatment of the two comorbidities.

In research, the COMCOLD index can be used to study effect modification, specifically the effect comorbidities have on treatment outcomes. Although it is currently well known that comorbidities are highly prevalent in patients with COPD, patients with comorbidities are often either excluded from clinical trials or their comorbidities are not considered for treatment effect analyses, which call into question the generalization of such results [35]. The COMCOLD index provides an efficient way to assess whether or not treatment effects vary according to the extent of multi-morbidity in previous and future COPD treatment trials.

5. Conclusion

Depression, anxiety, peripheral artery disease, cerebrovascular disease, and symptomatic heart disease had the greatest impact on health status of patients with COPD. The COMCOLD index reflects this impact and complements other comorbidity indices predicting death. The COMCOLD index may help clinicians to focus their attention on the most important comorbidities from a patients' perspective, and researchers may use the index to assess the impact of comorbidities in treatment effects.

Acknowledgments

We thank Ursula Schafroth (Horten Centre for patient-oriented research, University of Zurich, Switzerland) and Alice Karsten (Academic Medical Centre, Department of General Practice, University of Amsterdam, the Netherlands) and the participating general practitioners and patients with COPD in Switzerland and the Netherlands (Stichting Gezondheidscentra Amsterdam Zuidoost and Zorggroep Almere) who made this study possible by their enthusiastic participation.

Authors' contribution: A.F., P.M., N.P., L.S., M.Z., C.M.B., G.t.R., and M.A.P. contributed to conception and design of the study. P.M., L.S., and M.Z. conducted patient recruitment, patient enrollment, and data collection. M.A.P., A.F., and N.P. contributed to data verification and statistical analysis. M.A.P., A.F., G.t.R., C.M.B., N.P., L.S., and P.M. contributed to analysis and interpretation of data. A.F. and M.A.P. drafted the manuscript. All authors critical revised draft versions of articles and approved the final version.

References

[1] Crisafulli E, Gorgone P, Vagaggini B, Pagani M, Rossi G, Costa F, et al. Efficacy of standard rehabilitation in COPD outpatients with comorbidities. Eur Respir J 2010;36:1042−8.

[2] López Varela MV, Montes de Oca M, Halbert R, Muiño A, Tálamo C, Pérez-Padilla R, et al. Comorbidities and health status in individuals with and without COPD in five Latin American cities: the PLATINO study. Arch Bronconeumol 2013;49:468−74.

[3] Terzano C, Conti V, Di Stefano F, Petroianni A, Ceccarelli D, Graziani E, et al. Comorbidity, hospitalization, and mortality in COPD: results from a longitudinal study. Lung 2010;188:321−9.

[4] Corsonello A, Antonelli Incalzi R, Pistelli R, Pedone C, Bustacchini S, Lattanzio F. Comorbidities of chronic obstructive pulmonary disease. Curr Opin Pulm Med 2011;17:21−8.

[5] De Groot V, Beckerman H, Lankhorst GJ, Bouter LM. How to measure comorbidity. a critical review of available methods. J Clin Epidemiol 2003;56:221−9.

[6] Hall SF. A user's guide to selecting a comorbidity index for clinical research. J Clin Epidemiol 2006;59:849−55.

[7] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373−83.

[8] Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc 1968;16:622−6.

[9] Cleary PD, Greenfield S, Mulley AG, Pauker SG, Schroeder SA, Wexler L, et al. Variations in length of stay and outcomes for six medical and surgical conditions in Massachusetts and California. JAMA 1991;266:73−9.

[10] Kaplan MH, Feinstein AR. The importance of classifying initial comorbidity in evaluating the outcome of diabetes mellitus. J Chronic Dis 1974;27:387−404.

[11] Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2012;186:155−61.

[12] Smith K, Avis N, Assmann S. Distinguishing between quality of life and health status in quality of life research: a meta-analysis. Qual Life Res 1999;8:447−59.

[13] Balcells E, Gea J, Ferrer J, Serra I, Orozco-Levi M, de Batlle J, et al. Factors affecting the relationship between psychological status and

quality of life in COPD patients. Health Qual Life Outcomes 2010;8:108.
[14] Omachi TA, Katz PP, Yelin EH, Gregorich SE, Iribarren C, Blanc PD, et al. Depression and health-related quality of life in chronic obstructive pulmonary disease. Am J Med 2009;122:778.e9−778.e15.
[15] Van Manen JG, Bindels PJE, Dekker FW, Bottema BJAM, van der Zee JS, Ijzermans CJ, et al. The influence of COPD on health-related quality of life independent of the influence of comorbidity. J Clin Epidemiol 2003;56:1177−84.
[16] Van Manen JG, Bindels PJE, Dekker FW, Ijzermans CJ, Bottema BJAM, Van Der Zee JS, et al. Added value of co-morbidity in predicting health-related quality of life in COPD patients. Respir Med 2001;95:496−504.
[17] Wijnhoven HA, Kriegsman DM, Hesselink AE, de Haan M, Schellevis FG. The influence of co-morbidity on health-related quality of life in asthma and COPD patients. Respir Med 2003;97:468−75.
[18] Siebeling L, ter Riet G, van der Wal WM, Geskus RB, Zoller M, Muggensturm P, et al. ICE COLD ERIC−International collaborative effort on chronic obstructive lung disease: exacerbation risk index cohorts−study protocol for an international COPD cohort study. BMC Pulm Med 2009;9:15.
[19] Siebeling L, Puhan MA, Muggensturm P, Zoller M, Ter Riet G. Characteristics of Dutch and Swiss primary care COPD patients - baseline data of the ICE COLD ERIC study. Clin Epidemiol 2011;3:273−83.
[20] Puhan MA, Behnke M, Devereaux PJ, Montori VM, Braendli O, Frey M, et al. Measurement of agreement on health-related quality of life changes in response to respiratory rehabilitation by patients and physicians−a prospective study. Respir Med 2004;98:1195−202.
[21] Schunemann HJ, Griffith L, Jaeschke R, Goldstein R, Stubbing D, Guyatt GH. Evaluation of the minimal important difference for the feeling thermometer and the St. George's Respiratory Questionnaire in patients with chronic airflow obstruction. J Clin Epidemiol 2003;56:1170−6.
[22] The EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199−208.
[23] Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. Thorax 1987;42:773−8.
[24] Putcha N, Puhan MA, Hansel NN, Drummond MB, Boyd CM. Impact of co-morbidities on self-rated health in self-reported COPD: an analysis of NHANES 2001-2008. COPD 2013;10:324−32.
[25] Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2011: Available at http://www.cdc.gov/nchs/nhanes.htm Accessed May 2, 2013.
[26] Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145:247−54.
[27] Snaith RP. The hospital anxiety and depression scale. Health Qual Life Outcomes 2003;1:29.
[28] Crawford JR, Henry JD, Crombie C, Taylor EP. Normative data for the HADS from a large non-clinical sample. Br J Clin Psychol 2001;40:429−34.
[29] Ozalevli S, Ozden A, Itil O, Akkoclu A. Comparison of the sit-to-stand test with 6 min walk test in patients with chronic obstructive pulmonary disease. Respir Med 2007;101:286−93.
[30] Stel VS, Smit JH, Pluijm SMF, Visser M, Deeg DJH, Lips P. Comparison of the LASA Physical Activity Questionnaire with a 7-day diary and pedometer. J Clin Epidemiol 2004;57:252−8.
[31] Mukherjee B, Ou HT, Wang F, Erickson SR. A new comorbidity index: the health-related quality of life comorbidity index. J Clin Epidemiol 2011;64:309−19.
[32] Crisafulli E, Costi S, Luppi F, Cirelli G, Cilione C, Coletti O, et al. Role of comorbidities in a cohort of patients with COPD undergoing pulmonary rehabilitation. Thorax 2008;63:487−92.
[33] Tinetti ME, McAvay GJ, Chang SS, Newman AB, Fitzpatrick AL, Fried TR, et al. Contribution of multiple chronic conditions to universal health outcomes. J Am Geriatr Soc 2011;59:1686−91.
[34] Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. JAMA 2005;294:716−24.
[35] Boyd CM, Vollenweider D, Puhan MA. Informing evidence-based decision-making for patients with comorbidity: availability of necessary information in clinical trials for chronic diseases. PLoS One 2012;7:e41601.