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Original Research

Analysis of change in health-related quality of life in patients with COPD over 6 years, including information on dropouts: Results from the German COSYCONET cohort

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ABSTRACT

Introduction: Long-term studies as well as adequate methods accounting for attrition are necessary to measure the longitudinal change in health-related quality of life (HRQoL) in patients with chronic obstructive pulmonary disease (COPD). The aim of this analysis was to evaluate the change in HRQoL, measured by the EQ-5D-3L, over 6 years, while adequately accounting for dropouts.

Methods: We examined 6-year mean changes in HRQoL for 2701 COPD patients from the COSYCONET cohort study, based on data from baseline and follow-up visits after 1.5, 3, 4.5, and 6 years. Patients who dropped out during the 6-year follow-up were included in the analysis by imputing missing values using multiple imputation. We incorporated information on dropout reason in the imputation model and used additional information on HRQoL for dropouts to assess the imputation model.

Results: Average EQ-5D-3L deteriorated significantly by −0.121 (95 %-CI: 0.125; −0.117) over 6 years for all patients and by −0.047 (95 %-CI: 0.049; −0.045) when patients who dropped out because of death were excluded. Patients with impaired forced expiratory volume in 1 s (FEV_1) in percent of predicted normal values at baseline had a more pronounced 6-year mean decline in HRQoL. Inclusion of dropout information in the imputation model was informative. Assessment of the imputed data revealed that performing multiple imputation produced less biased results compared to complete case analysis.

Conclusion: The HRQoL decreased significantly over time for COPD patients. We propose a method to include all dropouts as well as additional information on dropouts to reduce bias in the results.

Abbreviations: 15D, 15-Dimensional Questionnaire; BMI, Body-Mass-Index; CI, Confidence Interval; COPD, Chronic Obstructive Pulmonary Disease; COSYCONET, COPD and Systemic Consequences – Comorbidities Network; DQ, Dropout Questionnaire; EQ-5D, EQ-5D-3L; FEV1 %pred, Forced Expiratory Volume in the First Second in Percent of Predicted Normal at Baseline; FMI, Fraction of Missing Information; FVC, Forced Vital Capacity; HRQoL, Health-Related Quality of Life; MICE, Multiple Imputation by Chained Equations; PMM, Predictive Mean Matching; POLR, Polytomous Regression for Ordered Data; SD, Standard Deviation; SGRQ, St George's Respiratory Questionnaire.

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a disease of major public-health relevance, with a 12-month prevalence of 5.8 % in Germany [1]. Patients with COPD usually experience a high burden of functional impairment and disease symptoms [2], which affect their health-related quality of life (HRQoL) in relation to disease severity [3].

Several studies have investigated the development of HRQoL in COPD patients cross-sectionally and longitudinally. Their focus was often on the correlation between the deterioration in HRQoL and the deterioration in lung function assessed via the forced expiratory volume in 1 s (FEV_1) [4–6], as well as on determinants of HRQoL [7], or the assessment of the HRQoL decline within clinical trial settings [8,9]. The decline in HRQoL was most commonly measured by the disease-specific St George's Respiratory Questionnaire (SGRQ), and only few studies determined the deterioration by generic instruments such as the 15-dimensional (15D) [10] or the visual analogue scale (VAS) of the EQ-5D [6]. Since comorbidities play an important role in COPD, Engström et al. [11] concluded that both, disease-specific and generic instruments, are relevant to assess the full spectrum of HRQoL in COPD patients.

Because COPD is a progressive disease, longitudinal studies with sufficiently large populations are necessary to assess its impact on HRQoL. As known, the major challenges of longitudinal studies are dropouts, resulting in missing values in the dataset. A common approach to deal with this is the analysis of complete cases only [12] but this may be heavily biased. One alternative method is multiple imputation of missing data, which seems to be suitable in longitudinal studies [13] and is suggested to lead to less biased results compared to complete case analysis [14].

Based on this, the aim of this analysis was to investigate the change in HRQoL as measured by the EQ-5D-3L (EQ-5D) over a 6-year period in patients with COPD, while including dropouts by multiple imputation and using data from the German COSYCONET (***CO**PD and **Sy**stemic Consequences – **Co**morbidities **Net**work*) cohort. Specifically, we compared the results of the imputation model and the complete case analysis. A novelty was the utilization of information on dropout reasons and of quality of life data from dropout questionnaires. We thus provide a statistical approach that might be useful for future studies. In addition to this algorithm, we aimed to identify potential determinants of the 6-year course of HRQoL, with emphasis on sex and baseline FEV_1.

2. Materials and methods

2.1. Study design

We analyzed baseline and follow-up data of the COSYCONET cohort, a prospective, multi-center cohort study in Germany. Between September 2010 and December 2013, a total of 2741 patients were recruited across 31 study centers distributed across Germany. Eligible patients needed to be aged $\geq$40 years and have a physician-based diagnosis of COPD. Patients with previous lung transplantation, lung volume reduction surgery and lung malignancies, as well as moderate to severe exacerbation in the previous four weeks were excluded. Details on the cohort and recruitment process have been published previously [15]. Patients were reassessed after 6 months and in addition every 18 months after the baseline visit. Due to the increasing number of dropouts, the last follow-up visit evaluated in this analysis was 6 years after the baseline examination, and subsequent visits were omitted. We also excluded 40 patients from the analysis because they did not have a fully reliable diagnosis of COPD according to information from the respective study centers. We kept participants in the analysis who had a ratio of FEV_1 over FVC (forced vital capacity) of $FEV_1/FVC \geq 0.7$ at baseline. Although these patients did not fulfill the formal GOLD criterion for COPD, all of them had a reliable diagnosis of COPD and it has been shown that these patients typically show all clinical signs of COPD [16]. Furthermore, a substantial proportion of these patients fulfilled the 0.7-criterion at some of the follow-up visits.

2.2. Outcome

The outcome of interest was HRQoL measured by the self-reported EQ-5D-3L questionnaire, which patients completed at baseline and each follow-up visit. The EQ-5D-3L is a generic HRQoL instrument with 243 (3^5) possible current health states based on five dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each with three levels (1: no problems, 2: some problems, 3: extreme problems). Patients were asked to select one number for each dimension, resulting in a five-digit number over all five dimensions, describing the patient's health state [17]. The time-trade-off tariff of Greiner et al. [18] was chosen – a tariff based on the valuation of given health states that reflect the preferences of the German population – to transform all possible health states to utility values. Thus, possible values range from −0.205 to 1, whereby higher values indicate better quality of life.

2.3. Covariables

Patients' age, sex, highest education level, and the sum of comorbidities were collected at baseline. Education was categorized into basic, secondary, or higher education. The sum of comorbidities was found to be sufficient as predictive factor [19] and was calculated from 33 self-reported physician-based comorbidities at baseline, including asthma, chronic bronchitis, hypertension, heart failure, stroke, diabetes mellitus, osteoporosis, and psychiatric disorders.

Spirometry was performed according to standard procedures [20,21] and the results were expressed as percent of predicted normal values (% predicted) using reference values of the Global Lung Function Initiative (GLI) [22]. Time-dependent covariables such as FEV_1 % predicted, exacerbation history, body-mass-index (BMI), and smoking status were collected at baseline and each follow-up visit. The most severe acute exacerbation in the past year was categorized as: No exacerbation, mild, moderate, severe. Mild exacerbations were defined as symptoms that required self-managed medication, moderate exacerbations as symptoms that required medical help, and severe exacerbations as symptoms that required hospitalization [23]. While exacerbations are an important determinant of quality of life, our focus was on unbiased longitudinal estimations of quality of life, which is why we did not specifically investigate the potential influence of exacerbations on quality of life. BMI was categorized into underweight (BMI $<$18.5 kg/m^2), normal weight (18.5 $\leq$ BMI $<$25), overweight (25 $\leq$ BMI $<$30), and obese (BMI $\geq$30). Smoking status comprised never smokers, current smokers, and former smokers. All of these variables were assessed at each follow-up visit.

After dropout from the study, each patient's dropout reason was collected by health care professionals interviewing the patients or family members. Answers were entered as open text and afterwards categorized in accordance with the coordinating center in Marburg. Patients were allocated to the following categories: *not reached* (could not be reached or stated that moving was the reason for discontinuation of the study), *too ill* (patients felt too ill to participate in the follow-up visits, were hospitalized or were in nursing care), *died, study center closed*, *unknown/not interested* (no time to participate in the study, or too much effort, or not interested in the continuation of the study, or unknown reason for discontinuation). Patients who completed the study until 6 years after the baseline visit were classified as *no dropout*.

Starting in 2017, dropout questionnaires (DQs) were sent to patients that dropped out from the study, assessing the EQ-5D as described above, among other information. Either the patients themselves, a care giver or a family member filled out the DQ. Of the 184 DQs returned, 59 were excluded, since the date of the completed DQ was more than 6 years after baseline visit and thus exceeded the analyzed study period.

One DQ provided an EQ-5D value for a patient who did not attend the 4.5-year follow-up and was therefore sent a DQ. Later, but before the next follow-up, the patient died and was therefore classified as dropout due to death. Thus, the DQ was excluded, leaving a total of 124 DQs for analysis.

2.4. Statistical analysis

We compared EQ-5D mean values at baseline and all follow-up visits cross-sectionally for complete cases, available cases, and imputed data. The 6-year EQ-5D mean change was computed for complete cases and for imputed data. Calculation of the 6-year mean change for available data was only possible for patients with EQ-5D values at baseline and 6-year-follow-up visit, resulting in the 6-year mean change of the complete case analysis. Complete case analysis comprised all patients that did not drop out from the study and had an EQ-5D value at each time point, whereas for available case analysis, mean values of all available EQ-5D values at each time point were computed, independent of whether patients continued the study at the following time point.

We also analyzed the 6-year mean changes stratified by sex and by FEV_1 % predicted category at baseline for imputed data, once for all patients and once for all patients who did not die during the study period. FEV_1 % predicted values were categorized after imputation for stratified analysis into the following groups according to the GOLD stages [24]: Very severe (FEV_1 % predicted <30 %), severe ($30\ \% \leq FEV_1$ % predicted <50 %), moderate ($50\ \% \leq FEV_1$ % predicted <80 %) and mild (FEV_1 % predicted ≥ 80 %).

All 6-year mean changes were assessed at 95 % significance level using paired t-tests. Data are presented as frequencies (%) for categorical variables, mean (±SD) for continuous variables, and the 6-year mean changes are presented as mean with confidence intervals (95 %-CIs), except if stated otherwise.

Additionally, we analyzed the correlation and mean difference between the imputed data and the available EQ-5D scores from the DQ for the 124 patients who completed the DQ. Correlation was assessed using Pearson's correlation coefficient. The EQ-5D values of the DQ were compared pairwise with the imputed EQ-5D value that was closest to the date of the DQ. To evaluate the representation of dropouts by complete case analysis, we computed the mean difference between the EQ-5D data from the DQ and the values from the complete case analysis for the corresponding time point.

2.5. Imputation model

We used multiple imputation by chained equations (MICE) to address missing values and create imputed datasets for the analysis. Each imputed dataset was the result of an iterative process, which allowed to handle multiple variables with missing values [25]. Multiple imputation was carried out with the R package 'mice' [26] and comprised two steps – first the imputation of the data, followed by the analysis of each dataset and pooling of the estimates from each dataset according to Rubin's Rule [27].

A total of 71 imputed datasets were created based on the highest proportion of missing values for the EQ-5D at the 6-year follow-up visit [25]. Further details on the derivation of the number of imputed datasets are available in Appendix A.

For patients who died, EQ-5D values could not be observed. Therefore, imputed values for these patients were not meaningful. The missing EQ-5D values of the remaining follow-up visits in those patients were therefore replaced by the value 0 after imputation was performed. The resulting distribution of the imputed EQ-5D values followed the distribution of the observed EQ-5D values (Figure B.1, Appendix B). To avoid underestimation of the mean EQ-5D values for the overall population, we performed the above specified analysis once for all patients, and once for all patients excluding those who died. For the latter, we also provide average EQ-5D values and 6-year mean changes conditional on survival.

Lastly, the EQ-5D means at each time point and their corresponding (within) variances were calculated for each dataset, as well as the between-variance, which describes the variance between the imputed datasets, and then pooled across the 71 imputed datasets using Rubin's rule [27].

2.6. Sensitivity analysis

To account for uncertainty due to imputation of missing values caused by dropout, we performed a sensitivity analysis by performing multiple imputation based on different variations of the above specified model. We excluded the dropout reason as explanatory variable (additional model 1, Table C.1. 1 and C.1. 2) to analyze the influence of additional information regarding the dropout mechanism. Furthermore, we included preceding FEV_1 % predicted and exacerbation values as explanatory variables (additional model 2, Table C.2. 1 and C.2. 2), and finally, we applied the specified imputation model to patients that participated in at least the first two study visits (baseline and 1.5-year follow-up visit) (additional model 3, Table C.3. 1).

All statistical analysis were performed using R version 4.2.2 [28].

3. Results

3.1. Patient population

A total of 2701 patients of the COSYCONET cohort were included in the present analysis. Of those, 2061 patients remained in the study until the first follow-up after 1.5 years, 1467 after 3 years, 1090 after 4.5 years, and 806 patients remained in the study until the end of the analyzed period. The most common reasons for dropout were lack of interest or other unspecified reasons ($N = 648$), being too ill ($N = 525$), death ($N = 273$), termination of the study center ($N = 270$), and loss to follow-up ($N = 179$). Fig. 1 illustrates the flow of patients through the study period of 6 years.

3.2. Patient characteristics at baseline

Patient characteristics at baseline, stratified by their dropout reason, are summarized in Table 1. Patients who died or felt too ill compared to those that did not drop out had a higher age (69 and 68 vs. 63 years), a lower baseline FEV_1 % predicted (47 and 49 vs. 63), and a lower baseline EQ-5D (0.78 and 0.78 vs. 0.84), respectively. Patients who died were more likely to be male than female. Compared to the overall population, patients that could not be reached, were no longer interested or had an unknown reason for dropout had a lower percentage of former smokers (59 % and 61 % vs. 68 %) and a higher percentage of current smokers (35 % and 30 % vs. 24 %), whereas patients who dropped out because the study center closed showed a higher percentage of former smokers (76 % vs. 68 %) and a lower percentage of current smokers (14 % vs. 24 %). Other characteristics for all three groups were similar to those of the overall population.

3.3. Analysis of 6-year mean change

First, we depicted the development of the mean EQ-5D for COPD patients for all available cases, all complete cases and after imputation for all patients, as well as for all patients in whom dropout was not caused by death (Fig. 2). Available case analysis comprised 2685 observations at baseline and 2041, 1418, 1040 and 767 patients at 1.5-year, 3-year, 4.5-year and 6-year follow-up visits, respectively. The mean EQ-5D for all available cases was 0.816 (±0.209) at baseline and 0.819 (±0.206) at the 6-year follow-up. Out of the 806 COPD patients who remain in the study until the 6-year follow-up, 703 had EQ-5D values at each visit. For those complete cases, the mean EQ-5D significantly decreased, with a change of −0.022 (95 %-CI: −0.026; −0.019) over the 6-year period. Analysis of all 2701 patients based on the

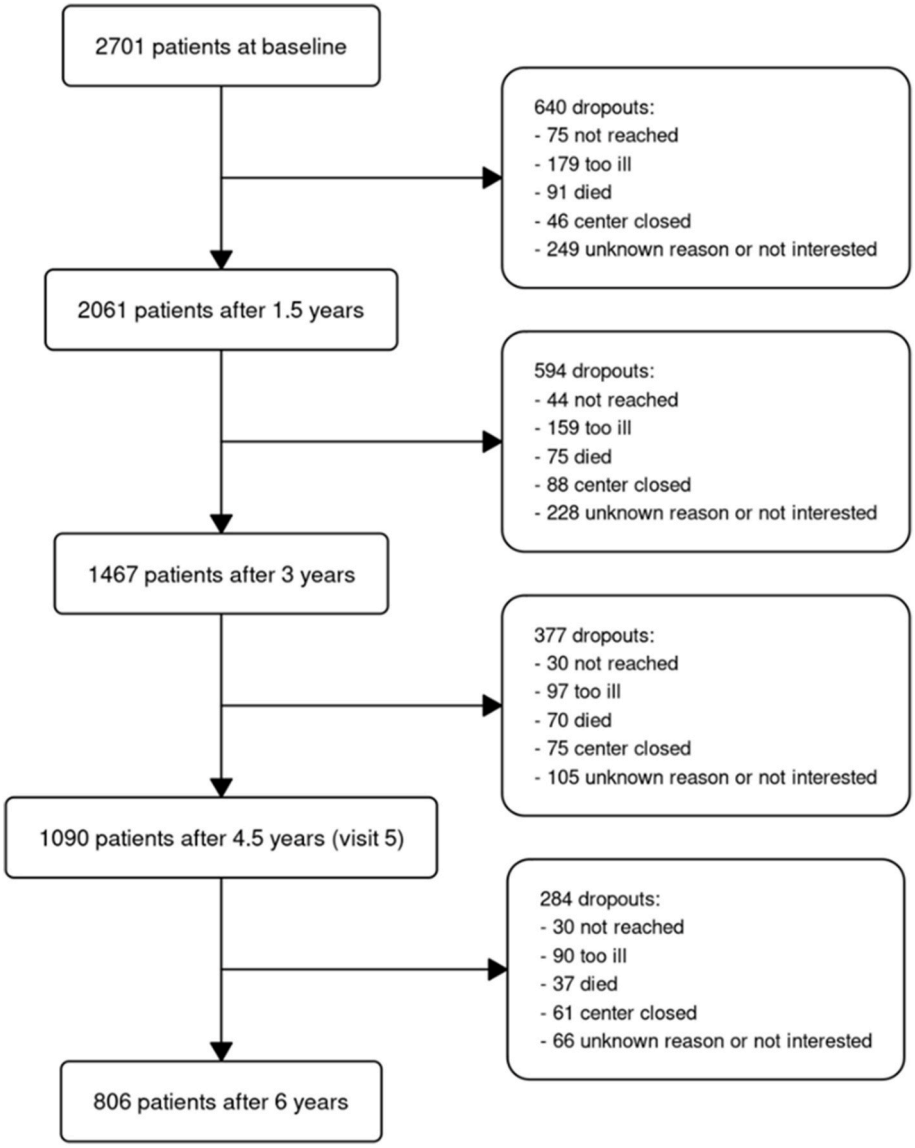

Fig. 1. Flow diagram of patients over the course of 6 years.

imputed data showed a significant 6-year mean change by −0.121 (95 %-CI: −0.125; −0.117). Excluding patients who died, the 6-year mean decrease by 0.047 for the remaining 2428 patients was still significantly different from zero (95 %-CI: −0.049; −0.045). Further details on the EQ-5D means are provided in Table B. 1 of Appendix B.

3.4. Analysis of imputed data stratified by sex

Men showed a higher mean EQ-5D at baseline than women, with a value of 0.825 (±0.199) vs. 0.803 (±0.222), and a lower mean EQ-5D after 6 years with a value of 0.685 (±0.335) vs. 0.709 (±0.306). The 6-year mean change was −0.139 (95 %-CI: −0.145; −0.134) for males compared to −0.094 (95 %-CI: −0.099; −0.089) for females. When patients who died were excluded, the EQ-5D was higher at baseline (0.827 ± 0.199 vs. 0.812 ± 0.214) and at 6-year follow-up (0.778 ± 0.235 vs. 0.766 ± 0.240) for male patients, while the mean EQ-5D change of −0.048 (95 %-CI: −0.051; −0.046) vs. −0.046 (95 %-CI: −0.049; −0.043) was similar between male and female patients. For further details see Fig. 3 and Table B. 2 of Appendix B.

3.5. Analysis of imputed data stratified by FEV1 %pred

There was a clear pattern towards a stronger decline in the EQ-5D with more advanced GOLD stage, with 6-year mean differences of −0.032, −0.097, −0.169, and −0.205 in stages 1, 2, 3, and 4, respectively. This trend was driven mainly by patients who died, resulting in no trend after exclusion of those patients (see Fig. 4). For further details see Table B. 3 of Appendix B.

3.6. Correlation and mean difference between imputed data and EQ-5D data from the DQ

To determine the validity of the imputation model, the correlation and mean difference between the imputed data and additional data from the DQ was assessed for 124 COPD patients. For 112 patients, the imputed EQ-5D at year 6 and for 12 patients the EQ-5D at year 4.5 after baseline was compared to the additional EQ-5D values from the DQ, based on the time at which the DQ was filled out since the baseline visit. We observed a correlation coefficient of 0.557. The imputed EQ-5D values were on average 0.042 points higher than the EQ-5D values from the DQ. Fig. 5 shows the corresponding scatterplot.

When comparing the EQ-5D data from the DQ to the data from the

Table 1
Patient characteristics at baseline.

Variable		Dropout Status					
	Overall N = 2701	No dropout N = 806	Not reached N = 179	Too ill N = 525	Died N = 273	Center closed N = 270	Unknown or not Interested N = 648
Sex							
Male	1602 (59 %)	468 (58 %)	110 (61 %)	300 (57 %)	191 (70 %)	167 (62 %)	366 (56 %)
Female	1099 (41 %)	338 (42 %)	69 (39 %)	225 (43 %)	82 (30 %)	103 (38 %)	282 (44 %)
Age	65 (±9)	63 (±8)	63 (±9)	68 (±8)	69 (±8)	65 (±9)	65 (±8)
BMI	27.0 (±5.4)	27.2 (±5.0)	27.3 (±5.6)	26.8 (±5.8)	26.5 (±5.4)	27.0 (±5.0)	27.1 (±5.6)
FEV1 %pred	56 (±21)	63 (±20)	55 (±20)	49 (±18)	47 (±18)	54 (±21)	59 (±22)
Exacerbations							
None	1249 (46 %)	423 (52 %)	77 (43 %)	199 (38 %)	110 (40 %)	130 (48 %)	310 (48 %)
Mild	135 (5.0 %)	44 (5.5 %)	11 (6.1 %)	33 (6.3 %)	9 (3.3 %)	10 (3.7 %)	28 (4.3 %)
Moderate	802 (30 %)	231 (29 %)	62 (35 %)	179 (34 %)	68 (25 %)	71 (26 %)	191 (30 %)
Severe	512 (19 %)	108 (13 %)	29 (16 %)	112 (21 %)	86 (32 %)	59 (22 %)	118 (18 %)
Sum of Comorbidities[1]	3.8 (±2.7)	3.8 (±2.7)	3.8 (±2.7)	4.2 (±2.6)	4.5 (±2.8)	3.3 (±2.3)	3.6 (±2.7)
Smoking Status							
Never	212 (7.9 %)	64 (7.9 %)	12 (6.7 %)	37 (7.1 %)	15 (5.5 %)	27 (10 %)	57 (8.8 %)
Former	1828 (68 %)	559 (69 %)	105 (59 %)	365 (70 %)	199 (73 %)	204 (76 %)	396 (61 %)
Current	657 (24 %)	183 (23 %)	62 (35 %)	121 (23 %)	59 (22 %)	38 (14 %)	194 (30 %)
EQ-5D at Baseline	0.82 (±0.21)	0.84 (±0.19)	0.81 (±0.21)	0.78 (±0.23)	0.78 (±0.23)	0.84 (±0.20)	0.82 (±0.20)
Education level							
Basic	1495 (55 %)	383 (47.5 %)	99 (55.3 %)	323 (61.5 %)	172 (63.0 %)	139 (51.5 %)	379 (58.5 %)
Secondary	729 (27 %)	253 (31.4 %)	56 (31.3 %)	128 (24.4 %)	61 (22.3 %)	81 (30.0 %)	150 (23.1 %)
Higher	477 (18 %)	170 (21.1 %)	24 (13.4 %)	74 (14.1 %)	40 (14.7 %)	50 (18.5 %)	119 (18.4 %)

Values are expressed as mean (±SD) or frequency (%); SD is the standard deviation; BMI is the body mass index, FEV1%pred is the forced expiratory volume in the first second in percent of predicted normal at baseline; Exacerbation type covers the severity of the most severe acute exacerbation in the past year.
[1]p value from two-sided *t*-test for difference in sum of comorbidities compared to "No dropout": 0.9816 (not reached), 0.0084 (too ill), 0.0001 (died), 0.0024 (center closed), 0.3046 (unknown or not interested).

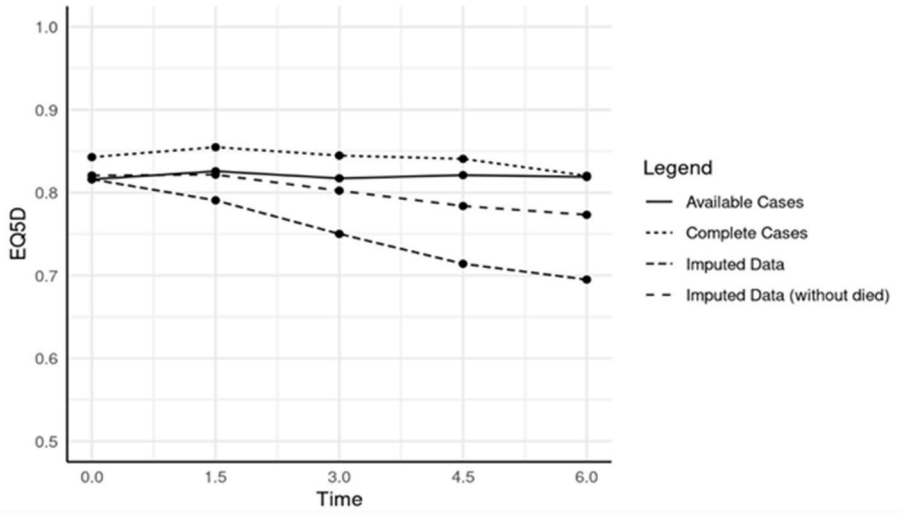

Fig. 2. Mean course of the EQ-5D over 6 years for all available cases, complete cases, imputed data and imputed data, excluding patients that died. Available case analysis comprised N = 2685 patients at baseline and N = 767 at 6-year follow-up; complete case analysis comprised N = 703 patients. Analysis of imputed data comprised N = 2701 patients and when patients that did drop out because of death were excluded N = 2428 patients. The y-axis is limited to a value range of 0.5–1.

complete cases, the latter resulted on average in mean EQ-5D estimates that were by 0.090 points higher than the EQ-5D values from the DQ.

3.7. Sensitivity analysis

Excluding the dropout reason as explanatory variable (additional model 1, Table C.1.1 and C.1.2 in **Appendix C**) resulted in slightly higher 6-year means as well as in slightly smaller 6-year mean decreases across all analyzed strata. This was also represented by the higher mean difference between the imputed EQ-5D data based on this model and the EQ-5D values from the DQ, with a value of 0.049 vs. 0.042 for the main model (with dropout reason).

Inclusion of preceding FEV_1 % predicted and exacerbation as explanatory variables (additional model 2, Table C.2.1 and C.2.2 in **Appendix C**) resulted in similar EQ-5D means at baseline and all follow-up visits, as well as for the 6-year mean decrease across all analyzed strata.

Performing analyses based on patients who participated at least at baseline and 1.5-year follow-up (additional model 3, Table C.3.1 and C.3.2 in **Appendix C**) led to higher overall baseline mean values of 0.828 (±0.200) vs. 0.816 (±0.209), 6-year mean values of 0.716 (±0.313) vs. 0.695 (±0.324), and a smaller 6-year mean decrease by −0.112 (95 %-CI: −0.116; −0.108) vs. −0.121 (95 %-CI: −0.125; −0.117). All variations of the imputation model resulted in similar correlations for the imputed EQ-5D values and EQ-5D values from the DQ.

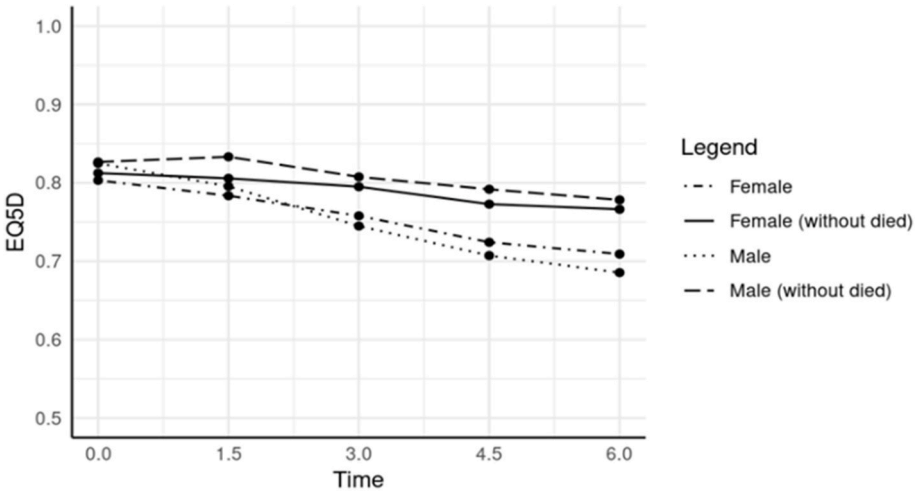

Fig. 3. EQ-5D means and 6-year mean differences after multiple imputation, stratified by sex.

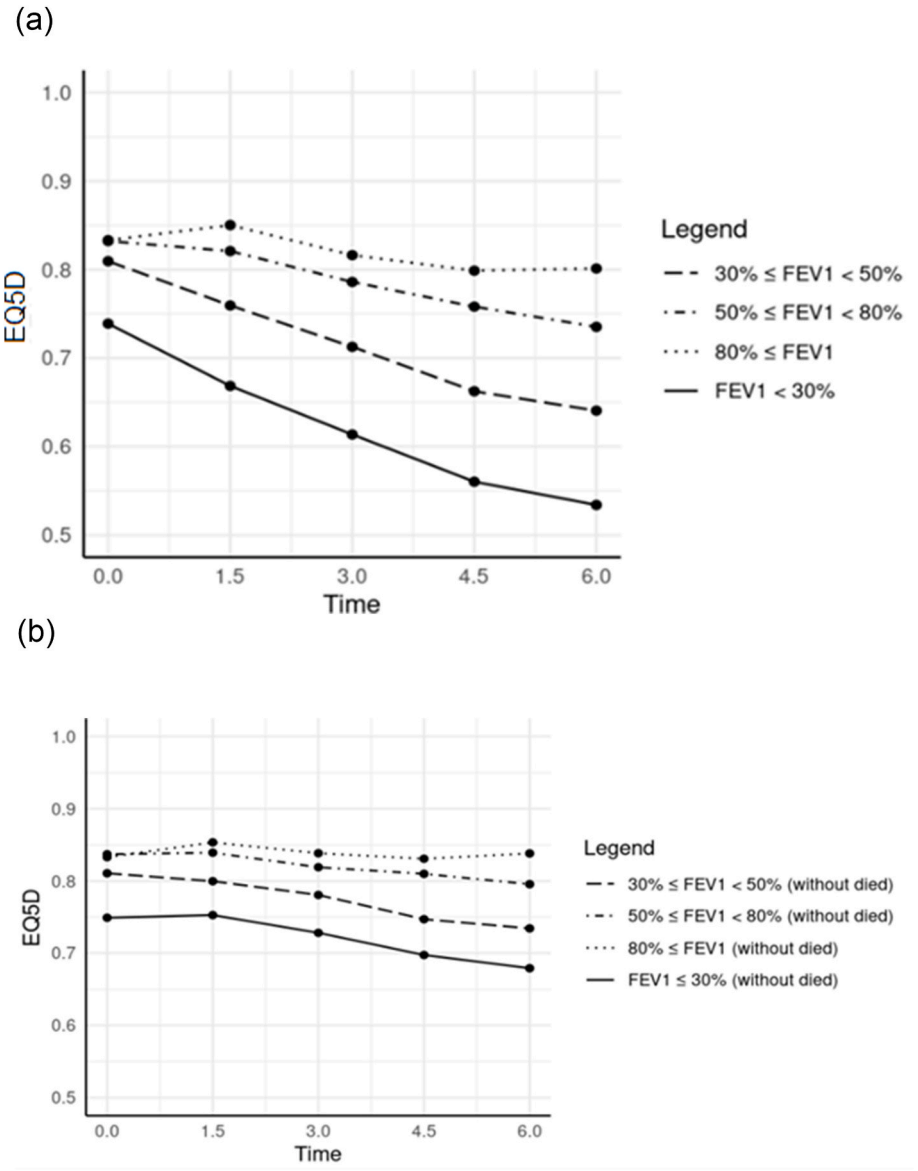

Fig. 4. EQ-5D means and 6-year mean differences after multiple imputation, stratified by FEV1.

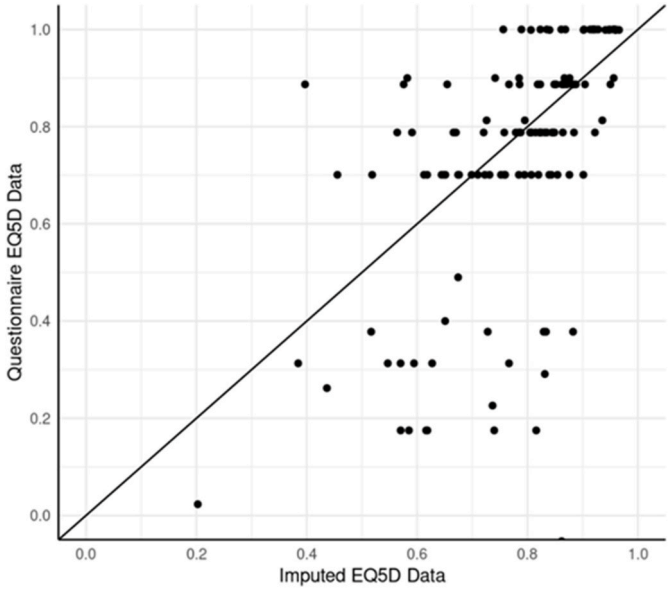

Fig. 5. Scatterplot of imputed EQ-5D data and EQ-5D data from the DQ (dropout questionnaire).

4. Discussion

In this study, health-related quality of life measured by the EQ-5D decreased significantly over the follow-up period of 6 years, with the strongest decrease in patients with strongly impaired lung function in terms of FEV_1 <50 % predicted at baseline. Furthermore, our results suggest that complete case analysis markedly underestimated the decline, while performing multiple imputation and the inclusion of additional information of patients who dropped out, such as the dropout reason, reduced the bias.

Patients diagnosed with COPD experienced a significant 6-year mean decline in HRQoL measured by the EQ-5D-3L by 0.121 and by 0.047 points when patients who died were excluded. The decrease by 0.121 was more than fivefold the mean decrease for complete cases (0.022). The difference can be explained by including patients who died or were too ill to continue the study in the imputation model. These patients already had lower EQ-5D scores at baseline. When comparing the mean difference of the imputed data and the EQ-5D values from the DQ (0.042) and the difference of the results from complete case analysis and values from the DQ (0.090), this suggested that the upward bias in estimated HRQoL by complete cases analysis could be reduced to half its value (0.042) by multiple imputation. A comparison of the magnitude of deterioration with previous results from the literature is difficult because of the use of differing tools for the HRQoL, differing study settings, and different approaches for analysis, such as complete case analyses [29,30]. Irrespective of this, our results are qualitatively in line with previous research indicating a decline in HRQoL of COPD patients when using the disease-specific SGRQ [31,32] and the generic 15D [4].

When analyzing different subgroups, we found that men had a significantly higher 6-year mean decrease in HRQoL than women. However, when excluding patients who died, the effect disappeared, which is consistent with previous research [33]. In our analysis, this was caused by assigning a HRQoL value of 0 to patients who died. Consequently, EQ-5D mean values were higher for men compared to women at all time points after excluding patients that died. Similar results of male patients reporting higher EQ-5D values than females have been published for other diseases, such as asthma [34]. Patients with baseline FEV_1 between 30 and 50 % or of <30 % predicted showed the strongest decrease in HRQoL measured by the EQ-5D. This association persisted after excluding patients who died. These results are in good agreement with previous findings of correlations between changes in FEV_1 % predicted and HRQoL [4,5].

For clinical practice, our findings imply that the decline in HRQoL in COPD is stronger than previously suggested. This further highlights the importance of investigating factors that might preserve HRQoL over a prolonged time period, such as smoking cessation, reducing the risk of acute exacerbations (e.g. by pneumococcal and influenza vaccination), “lung sports”, intensified treatment of comorbidities, etc.

Biering et al. [13] noted that no best practice exists for handling missing values due to death. Two approaches appear reasonable. From a health economics perspective, 1 represents full health, 0 represents death, and values below 0 indicate worse-than-death states [35]. From a medical perspective, the focus is on survival probability and HRQoL changes upon survival. In this analysis, for patients who dropped out due to death, missing EQ-5D values were imputed and replaced with 0 for subsequent visits. Sensitivity analysis showed that restricting the analyzed patient population to those who participated at least at baseline and 1.5-year follow-up, led to higher mean EQ-5D values and smaller 6-year mean differences. This was expected, because 640 patients who dropped out after the baseline visit were excluded from the analysis, of whom 179 patients felt too ill to continue the study and 91 patients died. Including these patients, as done in the main model, did therefore result in lower EQ-5D values.

Overall, EQ-5D mean values and 6-year mean changes were similar for the presented model variations within the sensitivity analysis and the differences could be explained. Interestingly, however, the mean difference between the imputed EQ-5D values and the EQ-5D values of the DQ were lowest for both models that included dropout reason as explanatory variable. This suggests that the inclusion of additional information on the dropout mechanism, as done in this analysis, reduced the bias in the imputation of EQ-5D values.

Interestingly, we found only minor differences in the sum of comorbidities according to dropout status. Several explanations are conceivable for this observation: First, the variable “sum of comorbidities” is a rather crude measure. It is conceivable that it does not fully reflect the burden of comorbidities, since their severity was not considered. Also, comorbidities likely differ in the extent by which they influence quality of life. Finally, the sum of comorbidities was recorded only at baseline any may have changed (likely increased) during follow-up. However, it appears to be rather commonly used and it has also been shown to be a significant predictor of quality of life in previous studies from the COSYCONET cohort [36]. Furthermore, considering the relatively high mean age of the study population at the first visit (65 years), it is likely that the number of comorbidities did not change drastically during the investigated study duration of 6 years.

Strengths of this study include its large sample size of 2701 patients in combination with the extensive follow-up period of 6 years. Thus, this study gives valuable insight into the course of HRQoL over time in COPD. Additionally, inclusion of dropouts into the analysis by using multiple imputation reduced bias compared to complete case analysis. Furthermore, information on the dropouts was used for validation, thereby enhancing the robustness of our results.

Several limitations may have influenced the results. Even though we observed an upward bias in mean EQ-5D values, this does not invalidate our findings of a stronger EQ-5D mean decrease than observed for complete case analysis. Presumably, the 6-year mean decrease might be even higher than the observed decrease, since imputed EQ-5D values were on average 0.042 points higher than the reported values from the DQ. However, the small amount of 124 DQ compared to the 1895 patients that dropped out limits the generalizability of these results. Attrition bias by differences between patients who sent the DQ back and those who did not, is conceivable. However, 12 of the DQs could be compared to imputed values at 4.5-year follow-up visit, and 112 to imputed values at 6-year follow-up, representing the most crucial time points, as they are the furthest away from the baseline visit and therefore give insight into the imputed EQ-5D values with the highest uncertainty. Another limitation of our study is the reliance on the categorization of

dropouts, which might not fully reflect the spectrum of dropout reasons or remain heterogeneous within the groups. For example, the category "too ill" might comprise patients with frequent exacerbations, but also patients with temporary or permanent deteriorations regarding comorbidities.

Although beyond the scope of this manuscript, alternative methods for longitudinal analysis of quality of life exist. For example, linear mixed models (mixed effects models), Generalized Estimating Equations (GEE) and inverse probability weighting (IPW) can be used to estimate the trend in quality of life, also with consideration of dropout reason and other factors.

In conclusion, HRQoL decreased markedly over time in COPD patients. Complete case analysis underestimated the effect by meaningful margins and should only be used as additional analysis. This has important implications for health-economic modeling, e.g., when calculating quality-adjusted life years (QALYs). Thus, studies of HRQoL should aim at including all dropouts in an appropriate model. Collecting and including additional information into the analysis can reduce bias and provide helpful insight into the validation of such models. Further research should focus on ways to effectively gain additional information on the dropout mechanism that can be used as auxiliary variables in the analysis.

CRediT authorship contribution statement

Celina Fahrenberg: Writing – original draft, Visualization, Methodology, Formal analysis. **Tobias Niedermaier:** Writing – review & editing. **Peter Alter:** Writing – review & editing. **Rudolf A. Jörres:** Writing – review & editing. **Claus F. Vogelmeier:** Writing – review & editing, Resources, Project administration. **Rolf Holle:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Ethics approval and consent to participate

The COSYCONET study was approved by the Ethics Committees of the local study centers and the Ethics committee of the University of Marburg as coordinating center and is registered on ClinicalTrials.gov (registration number: NCT1245933). All cohort patients provided their written informed consent.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used the large language model DeepL Write in order to improve the quality of writing. After using this tool, the author(s) reviewed and edited the content as needed and take full responsibility for the content of the published article.

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Declaration of competing interest

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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.2025.108153.

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