Respiratory Medicine 247 (2025) 108280

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Original Research

Parametric estimation of age-, sex-, and spirometry grade-specific mortality in a cohort of COPD patients from Germany: Results from COSYCONET

Tobias Niedermaier [a,*], Peter Alter [b], Rudolf Jörres [c,d,e], Claus Vogelmeier [f], Rolf Holle [a]

[a] Institute for Medical Information Processing, Biometry, and Epidemiology (IBE), Ludwig-Maximilians-Universität (LMU) Munich, 81377, München, Germany
[b] Department of Medicine, Pulmonary, Critical Care and Sleep Medicine, Philipps University of Marburg (UMR), German Center for Lung Research (DZL), Baldingerstrasse 1, Marburg, Germany
[c] Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, University Hospital, LMU Munich, Ziemssenstraße 1, Munich, 80336, Germany
[d] Comprehensive Pneumology Center Munich (CPC-M), Marchioninistr. 15, Munich, 81377, Germany
[e] German Center for Lung Research (DZL), Max-Lebsche-Platz 31, 81377, Munich, Germany
[f] Department of Medicine, Pulmonary, and Critical Care Medicine, German Center for Lung Research (DZL), University of Marburg, Hans-Meerwein-Straße 2, Marburg, 35043, Marburg, Germany

ARTICLE INFO

Keywords:
COPD
PRISm
Parametric survival
Markov model parameters

ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) substantially contributes to morbidity and mortality worldwide. We aimed at estimating Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric grade-specific mortality in COPD for Germany, using data from a large-scale cohort of patients with COPD.
Methods: Using COSYCONET data, a cohort of 2741 patients diagnosed with COPD was followed over up to 9 years. We estimated mortality rates for GOLD grades 1 to 4 and stratified into age and sex groups. An exponential survival model was used to estimate mortality after checking model assumptions. Additionally, a Cox proportional hazards model was estimated as plausibility check for the exponential model.
Results: A total of 345 deaths were observed during the follow-up period. The data fitted well to an exponential survival model when the first year of follow-up was excluded, suggesting a “healthy participant effect”. GOLD grade was a strong predictor of mortality, with hazard ratios of 1.6, 3.2, and 8.8 for GOLD 2–4 compared to GOLD 1. Hazard ratios of the Cox model were similar (1.7, 3.4, and 10.0 for grades 2–4 compared to grade 1). At a given grade, mortality strongly increased with age. 1-year mortality ranged from 0.5 % (GOLD 1, <55 years, females) to 54.9 % (GOLD 4, 80+ years, males). Mortality was lower among females by approximately 25 %.
Conclusion: Based on our findings, mortality in COPD depends on GOLD grade, age, sex and smoking status. Parametric estimation allowed to estimate 1-year mortality for each combination of COPD grade and age group, including uncertainty estimates.

Study highlights:

What is already known.

- Chronic obstructive pulmonary disease (COPD) is a major cause of death, and more advanced COPD grades are associated with poorer survival.
- Age, smoking, comorbidities and acute exacerbations are further important predictors of mortality.
- Mortality rates according to spirometric grade, sex and age are crucial input parameters for Markov models in order to estimate the long-term health consequences and economic impact of COPD on a population level.

What this study adds.

- We estimated 1-year mortality rates along with 95 % confidence intervals for COPD according to Global Initiative for Chronic

Abbreviations: COPD, Chronic obstructive pulmonary disease; COSYCONET, German COPD and Systemic Consequences – Comorbidities Network; FEV_1, Forced expiratory volume in 1 s; GOLD, Global Initiative for Chronic Obstructive Lung Disease; SE, Standard error; CI, Confidence interval; NA, Not applicable.

* Corresponding author.
E-mail address: tobias.niedermaier@ibe.med.uni-muenchen.de (T. Niedermaier).

https://doi.org/10.1016/j.rmed.2025.108280
Received 4 February 2025; Received in revised form 24 July 2025; Accepted 28 July 2025
Available online 29 July 2025

Obstructive Lung Disease (GOLD) grades 1–4, using an exponential (parametric) survival model.
- Estimated 1-year mortality rates ranged from 0.5 % (females, GOLD 1, <55 years) to 55 % (males, GOLD 4, 80+ years). Within each age group, there was a strong gradient in mortality according to grade.
- Ignoring the first year after patient recruitment improved model fit and reduced the "healthy participant effect".

1. Introduction

Chronic obstructive pulmonary disease (COPD) ranks among the top three causes of death globally [1]. In Germany, it is one of the most common causes of death, with approximately 30,000 deaths per year [2]. The prognosis of COPD is influenced by several factors, including more advanced spirometric GOLD (Global Initiative for Chronic Obstructive Lung Disease) grade (i.e., lower forced expiratory volume in 1 s [FEV_1]), dyspnea, lower exercise capacity, smoking, and cachexia [3].

Markov models, such as the lifetime COPD model by Menn et al. [21], can be used to project and compare long-term costs and health consequences e.g. of different treatments. Among other parameters like costs, utilities, and progression rates, accurate estimates for mortality according to age and grade are crucial inputs for such models. Numerous studies across various countries have established a strong association between GOLD grade and mortality risk [4–17]. However, only few studies have reported on the joint association between age and GOLD grade and mortality [18–20], and only one of them [20] also stratified by sex. Furthermore, existing studies have several drawbacks when using their results to derive parameters for a Markov model. Common limitations include insufficient case numbers for individual disease grades, and combining multiple grades into single categories (e.g., GOLD III and IV), or the use of uncommon reference groups (e.g. GOLD IV). In addition, Markov models require mortality rates that are assumed to be derived from an exponential survival model, whereas most studies on COPD mortality reported hazard ratios from a semi-parametric Cox model.

Our objectives were to estimate mortality rates for different combinations of GOLD grades, sex and age groups and to use these results to update the mortality parameters of a COPD Markov model previously established by Menn et al. [21]. To address this objective, we analyzed data from a 9-year follow-up of a large clinical COPD cohort from Germany.

2. Methods

2.1. Study design

The present analysis is based on the COSYCONET study (**CO**PD – **sy**stemic **con**sequences and comorbidities **net**work), a large prospective observational cohort study of COPD patients conducted across 31 study centers in Germany (Trial registration: NCT01245933). Detailed descriptions of the study design and methodology have been published previously [22,23]. To be eligible for enrollment, patients had to be aged 40 years or older, with a diagnosis of COPD or chronic bronchitis. Key exclusion criteria were major lung surgery, lung tumor, moderate or severe exacerbation in the past 4 weeks, or inability to walk or to understand the intention of the study. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and has been approved by the ethics committees of the participating centers and by the concerned data security authority. All participants provided written informed consent.

At the initial study visit and the follow-up visits, a broad set of functional and clinical assessments were performed [22]. For the current analysis, only data on age and sex, smoking history, and on disease stage categorized by GOLD grades [24] were used. As additional variables to characterize the cohort, we used exacerbation history (severity), and quality of life (Saint George's Respiratory Questionnaire [SGRQ] [25], 3-level version of the EQ-5D (EQ-5D-3L)). Predicted values for spirometry were taken from the GLI consortium [26].

2.2. Mortality and dropout (censoring) data

We focused on all-cause mortality as primary outcome because it is more reliable to establish than cause-specific mortality. Moreover, in decision modelling, all existing Markov models use all-cause mortality instead of disease-specific mortality because it reflects the patient-centered perspective.

If a patient missed one of the follow-up visits (6, 18, 36, 54, 72, 90 months after inclusion), the research assistants ascertained survival status (and, in the case of death, date of death) by contacting relatives, GPs, and hospitals. If the exact date of death was not available for a deceased patient, we applied midpoint imputation, i.e. the mean date between the date of the last visit and the next scheduled visit was assumed as date of death. For participants who withdrew from the study for reasons other than death, the date of their last completed visit was used as the censoring date.

2.3. GOLD classification

This analysis uses the well-established spirometric GOLD classification of grades 1–4, which has been maintained across all revisions and extensions of classifications over time. This classification also allowed to align with the structure of the Markov model, which assumes progressive transitions from one grade to the next. The updated systems (GOLD A–D classifications) based on a combination of symptoms and exacerbation severity have been shown to be less stable over time, as they depend on disease aspects that are more variable such as number of symptoms (Medical Research Council [MRC] dyspnea scale) and frequency of exacerbations [11].

Formally, the GOLD 1–4 classification requires a FEV_1/FVC ratio (Tiffeneau index) < 0.70 as indicator of airway obstruction. However, we also included 398 COSYCONET patients who did not fulfill this criterion at baseline (former GOLD 0). The reason is that these patients had a COPD diagnosis from their GP or specialist for more than one year and were treated accordingly. In addition, they also showed a spectrum of comorbidities typical for COPD [27], and a substantial part of these patients showed a FEV_1/FVC ratio of <0.70 over one of the subsequent study visits.

2.4. Statistical analysis

Cumulative mortality was estimated using the Kaplan-Meier method, with survival curves stratified by GOLD grades 1–4 (FEV_1 % predicted >80 %, 80– >50 %, 50– >30 %, and ≤30 % for grades 1, 2, 3, and 4, respectively). Participants with FEV_1/FVC ratio ≥ 0.70 were also assigned to GOLD 1–4 grades according to their FEV_1 levels.

In a Markov model, a constant annual mortality rate is assumed for GOLD grade 1–4. However, in our model, this rate increases when a patient transitions to a different 5-year age group, whereby age groups were chosen as 40–54, 55–59, …, 75–79, and 80+ years. A constant mortality rate implies an exponential distribution of survival times, so we estimated the mortality rates using a parametric exponential model applied to survival data from the COSYCONET cohort over a 5-year period. Model diagnostics, such as plotting -ln S(t) versus time t, were used to check how well the data fitted the exponential survival model. This was the case when the first and the last year of follow-up were excluded (for details see Results). However, all available data (from inception onward including the last year) were used in a sensitivity analysis. In further sensitivity analyses, we restricted the analysis to COPD patients of GOLD grades 1–4 and a FEV_1/FVC ratio of <0.70. The exponential survival model included GOLD grade, age (in 5-year groups) and sex as covariables. Using the "predict" function in R, we derived 1-year mortality rates for every combination of grade, age group and sex. This was the main outcome because those grade-, age group- and sex-specific rates are necessary input parameters for our Markov model. We additionally assessed the impact of smoking on mortality by deriving mortality rates stratified by smoking status and GOLD stage. To verify the robustness of the results, we also conducted semi-parametric Cox proportional hazards regression to estimate mutually adjusted (multivariable) hazard ratios for GOLD grade, sex and age.

We used R version 4.4.2 (R Core Team (2024). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria) for all statistical analyses. The R packages used were "survival" (version 3.7-0) for analysis and "survminer" (version 0.4.9) for visualization. Parametric survival models were estimated with the "flexsurv" package (version 2.3.2).

3. Results

3.1. Study population characteristics at baseline

The study population (see Table 1) comprised 2741 participants, of which 40 were excluded because their COPD diagnosis was not confirmed by symptoms at the time of the study. Of the remaining 2701 participants, the mean age at baseline was 65.1 years, and approximately 60 % were male. Approximately 8 % of the patients had never smoked, whereas 68 % were former and 24 % were current smokers. Numbers of participants stratified by grade are shown in Fig. 1. Age distribution varied across GOLD grades, with younger participants (<55 years) more prevalent in GOLD 1 and GOLD 2, while GOLD 3 and GOLD 4 had a higher proportion of participants aged 65 years and older.

3.2. Factors associated with mortality

During the 9 years of follow-up, 345 deaths were recorded. Non-parametric Kaplan-Meier survival curves stratified by GOLD grade from end of year 1 to year 7.5 are shown in Fig. 2 (top). Survival was poorest in grade 4, and progressively better in grades 3, 2, and 1. Mortality was not reliably recorded for follow-up durations >7.5 years, leading to potentially inaccurate survival estimates in that time interval. When including all available follow-up and mortality data in sensitivity analysis, the overall pattern remained, but the drop in the survival curves became steeper towards the final 2 years of follow-up (Fig. 2, bottom).

Parametric exponential survival models, excluding data from the first year and censoring after 7.5 years, demonstrated a good fit to observed survival data (Fig. 3). By comparison, when fitting an exponential model over the complete 9 years of follow-up (Supplementary Fig. 1), we observed that the exponential distribution did not fit well the observed data in the first year (where observed survival was better than expected) and the last 1–2 years (where survival was worse than previously predicted).

The parametric survival indicated that mortality increased strongly with grade, with hazard ratios of 1.6, 3.2, and 8.7 (Table 2, left). Age and sex were also strongly and independently associated with mortality. A gradual increase in hazard ratios was observed from 0.3 (40–54 years) to up to 4.0 (80+ years). At a given grade and age group, mortality was higher among males than females by approximately 1/3. Results of the Cox model (Table 2, right) were very similar to those of the exponential model. Only for grade 4 (HR 9.7) and the age group 80+ years (HR 4.9), estimates differed by more than 10 %. Results of analogous models with additional adjustment for smoking history are shown in Supplementary Table 1. In those models, former and never smoking were associated with significantly lower mortality. Risk estimates for sex remained virtually unchanged. By contrast, hazard ratios for the other estimates were qualitatively similar but suggested slightly stronger associations (e.g. HRs of 11–12 for GOLD grade 4).

3.3. Mortality rates

Numeric estimates for 1-year mortality including 95 % confidence intervals for the main and sensitivity analyses are shown in Table 3 (excluding the first and last year of follow-up). Estimated 1-year mortality rates ranged from 0.51 % (females, <55 years, GOLD 1) to 54.9 % (males, GOLD 4, 80+ years). Sensitivity analyses including the first and the last year of follow-up yielded trends consistent with this (Supplementary Table 2). In further sensitivity analysis, we excluded participants which may be classified as PRISm or pre-COPD according to the FEV_1/FVC ratio, i.e., symptomatic individuals with FEV_1/FVC ratio at baseline being >0.7. As shown in Supplementary Table 3, the resulting mortality estimates were generally somewhat lower than when including those participants, but in most cases estimates differed by less than 10 %. Only for GOLD grade 1, mortality increased considerably, suggesting that the subgroup with FEV_1/FVC >0.7 may include some patients with questionable COPD diagnosis. This is also in agreement with hazard ratios which showed a smaller spread between GOLD grades

Table 1
Study population description (N = 2701, participants assigned to GOLD grades according to FEV_1, irrespective of FEV_1/FVC ratio).

Baseline characteristics	Total N	%	GOLD 1	%	GOLD 2	%	GOLD 3	%	GOLD 4	%
Age (years)										
<55	327	12.1	60	14.8	121	10.6	98	11.0	46	18.3
55-<65	884	32.7	115	28.4	351	30.8	307	34.5	108	42.9
65-<75	1154	42.7	171	42.2	504	44.2	389	43.8	81	32.1
≥75	336	12.4	59	14.6	163	14.3	95	10.7	17	6.7
Sex										
Male	1602	59.3	220	54.3	674	59.2	539	60.6	162	64.3
Female	1099	40.7	185	45.7	465	40.8	350	39.4	90	35.7
Smoking status										
Current	657	24.4	114	28.1	309	27.2	194	21.8	36	14.3
Former	1828	67.8	240	59.3	733	64.5	642	72.3	202	80.5
Never	212	7.9	51	12.6	95	8.4	52	5.9	13	5.2
EQ-5D-3L (mean, SD)	0.8161	(0.209)	0.833	(0.203)	0.832	(0.203)	0.809	(0.208)	0.738	(0.239)
SGRQ (mean, SD)	42.9	(20.0)	30.8	(17.6)	39.5	(19.2)	48.5	(17.9)	58.2	(18.2)
AE severity (most severe AE in the previous 12 months)										
None	1249	46.3	250	61.7	588	51.6	330	37.2	68	27.0
Mild only	135	5.0	17	4.2	73	6.4	35	4.0	10	4.0
Moderate	802	29.7	108	26.7	323	28.4	295	33.3	74	29.4
Severe	512	19.0	30	7.4	155	13.6	226	25.5	100	39.7

Abbreviations: AE, acute exacerbation; COPD, chronic obstructive pulmonary disease; FEV_1, Forced expiratory volume in 1 s; GOLD, Global Initiative For Chronic Obstructive Lung Disease; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire.

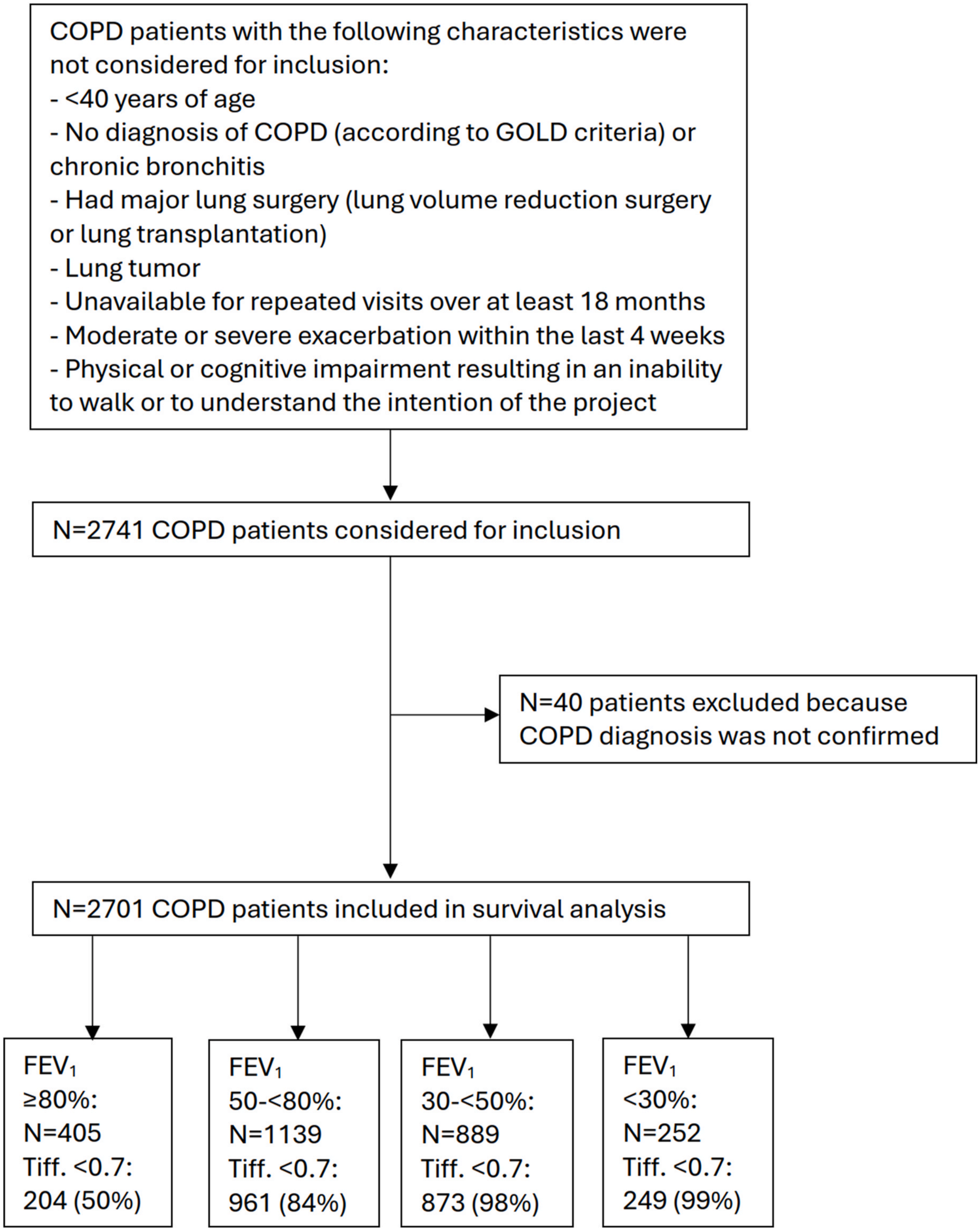

Fig. 1. Flow-Diagram of study participants.

(see Supplementary Table 4) than in the main analysis. When stratifying by smoking status, we observed distinctly lower mortality rates among former smokers and even more so among never smokers, compared to current smokers (Supplementary Table 5). Finally, including severity of AEs in the models did not alter the remaining coefficients meaningfully, although estimates for GOLD grade were slightly attenuated (Supplementary Table 6).

4. Discussion

In this study of 2741 patients from Germany with the diagnosis of COPD (either of GOLD grades 1–4 or the former grade 0), we investigated survival patterns according to GOLD grade using Kaplan-Meier, parametric (exponential) and semi-parametric (Cox) survival models. Our results showed a graded relationship between GOLD grade and survival. Survival was poorest in GOLD grade 4 and improved progressively across grades 3, 2, and 1, though differences between grades 1 and 2 were relatively small. Male sex was a strong risk factor for mortality,

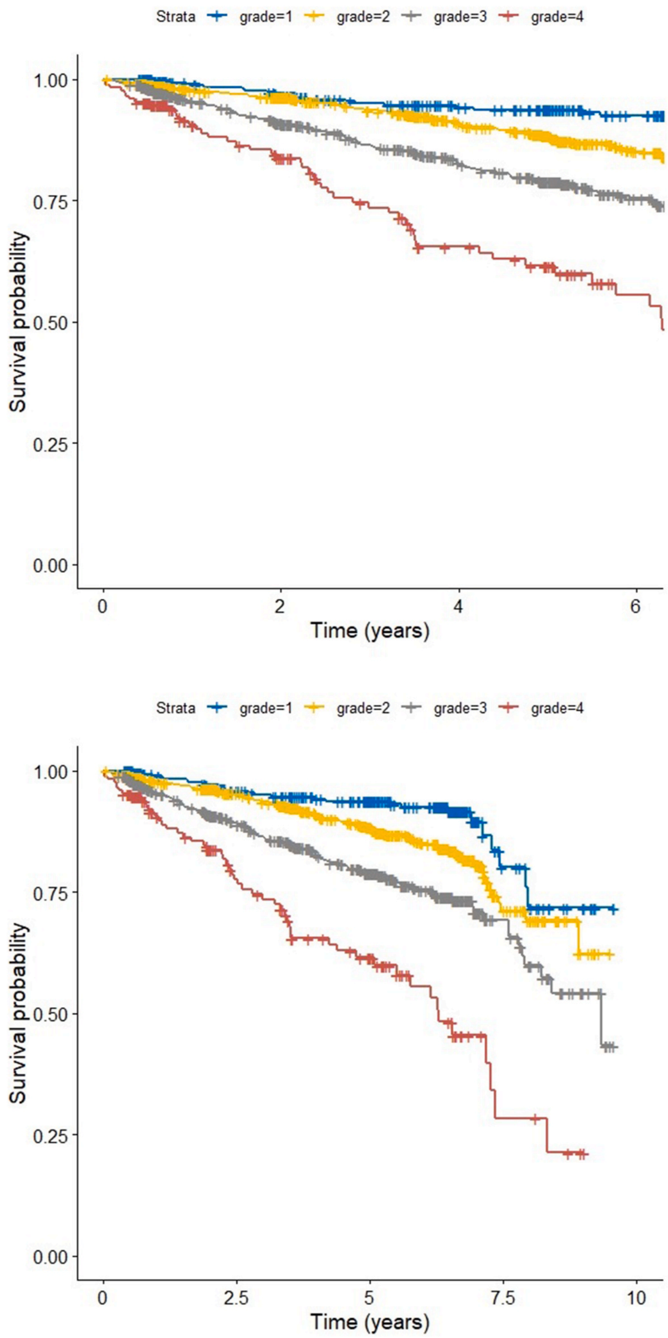

Fig. 2. Survival curves for COPD patients restricted to 7.5 years of follow-up in those who survived for at least 12 months (top) and over the entire COSYCONET cohort and study duration (bottom), stratified by GOLD grade.

independently of GOLD grade and age. Similarly, mortality strongly increased with age, independently of GOLD grade and sex. Smokers showed the highest mortality, followed by former smokers, whereas the lowest mortality was observed among never smokers.

Compared to other studies investigating mortality among COPD patients, our study differs in several important aspects. First, our aim was not primarily to estimate survival rates at specific time points using Kaplan-Meier plots. Instead, we focused on annual mortality rates which are assumed to be constant in a Markov model. Thus, we used a parametric (exponential) survival model, adjusted for grade, age, and sex. Our focus was also not on predictors of mortality. Instead, the association between those factors and mortality was used to derive estimates for 1-year mortality according to grade, age and sex for the Markov model.

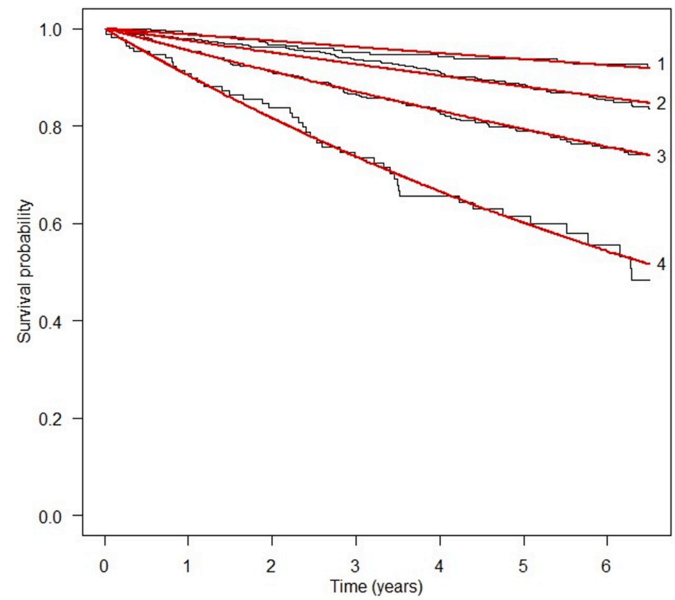

Fig. 3. Parametric survival curves, stratified by GOLD grades 1–4, excluding first year and censoring >7.5 years of follow-up.

Corresponding 95 % confidence intervals can be translated into model parameters for probabilistic sensitivity analyses.

Furthermore, we observed that in the first year and at the end of follow-up, the exponential distribution did not fit well with the observed pattern. Participants in a terminal condition were not eligible for study recruitment, leading to a short initial “plateau” phase in survival curves. To avoid an underestimation of mortality rates over the entire follow-up, we thus excluded the first year of follow-up in the main analysis, which considerably improved the model fit. Furthermore, we also restricted follow-up to a maximum of 7.5 years because most study centers no longer participated after that time and follow-up information (including mortality) was thus less reliable than before.

When excluding patients with FEV_1/FVC ratio $\geq$0.70, mortality rates in GOLD grade 1 increased, whereas estimates did not change substantially in the other grades. As can be seen in Fig. 1, only GOLD grade 1 comprised a considerable proportion of patients with FEV_1/FVC ratio $\geq$0.70, and as already stated, all patients had a physician diagnosis of COPD and several of these showed a FEV_1/FVC ratio <0.70 at a subsequent study visit. Still, it might be questioned if all of these patients have been correctly diagnosed. While an in-depth analysis and discussion of the mortality patterns for patients categorized as Pre-COPD or PRISm are beyond the scope of this manuscript, future analyses should investigate mortality for those groups in comparison to COPD. Previous studies mostly suggested that mortality in PRISm patients is similar to that of COPD patients in grades GOLD 2 [28] or 1–2 [29–32]. One study reported even higher all-cause mortality with PRISm compared to COPD [33].

Our findings confirm and extend previous research demonstrating the strong association between GOLD grade and mortality [4–17,19,20,34–36]. While prior studies have often focused on a combination of grades, such as GOLD 2–4 [16] or 3 + 4 [35], or the GOLD A-D classification, our analysis provides survival estimates for each individual grade (1–4). Moreover, we addressed methodological limitations noted in earlier studies, such as small sample size, by using a large, nationally representative cohort and by incorporating sensitivity analyses. The relatively high survival rates in the first year of follow-up might result from exclusion of patients with recent moderate or severe exacerbations.

Gedebjerg et al. [11] estimated cumulative all-cause and respiratory 1-year and 3-year mortality among almost 34,000 patients in Denmark based on both, the GOLD 2007 (1–4) and GOLD 2017 (A-D)

Table 2

Results of the parametric (exponential) survival model (left) and the Cox proportional hazard model (hazard ratios, right), along with 95 % confidence intervals and P values. *Results were obtained excluding the first and last year of follow-up.*

	Parametric (exponential) survival model		Cox proportional hazard model	
Variable	Hazard ratio (95 % CI)	P value	Hazard ratio (95 % CI)	P value
Grade 1	1 (Ref.)	–	1 (Ref.)	–
Grade 2	1.616 (1.052–2.483)	0.0284	1.664 (1.083–2.557)	0.0202
Grade 3	3.184 (2.077–4.880)	<0.0001	3.285 (2.142–5.037)	<0.0001
Grade 4	8.802 (5.467–14.170)	<0.0001	9.678 (5.993–15.630)	<0.0001
Male sex	1.369 (1.070–1.751)	0.0124	1.392 (1.088–1.781)	0.0086
40–54 years	0.302 (0.179–0.511)	<0.0001	0.297 (0.175–0.502)	<0.0001
55–59 years	0.402 (0.253–0.639)	0.0001	0.406 (0.256–0.645)	0.0001
60–64 years	0.540 (0.376–0.777)	0.0009	0.524 (0.364–0.755)	0.0005
65–69 years	1 (Ref.)	–	1 (Ref.)	–
70–74 years	1.039 (0.761–1.420)	0.8092	1.056 (0.772–1.443)	0.7333
75–79 years	1.570 (1.051–2.345)	0.0273	1.606 (1.075–2.399)	0.0208
80+ years	4.160 (2.633–6.572)	<0.0001	4.872 (3.070–7.731)	<0.0001

The following results were obtained when including the entire study period:

	Parametric (exponential) survival model		Cox proportional hazard model	
Variable	Hazard ratio (95 % CI)	P value	Hazard ratio (95 % CI)	P value
Grade 1	1 (Ref.)	–	1 (Ref.)	–
Grade 2	1.655 (1.088–2.516)	0.0186	1.711 (1.125–2.604)	0.0121
Grade 3	3.388 (2.240–5.124)	<0.0001	3.633 (2.401–5.499)	<0.0001
Grade 4	8.869 (5.618–14.003)	<0.0001	10.475 (6.612–16.594)	<0.0001
Male sex	1.330 (1.056–1.675)	0.0153	1.361 (1.080–1.714)	0.0090
40–54 years	0.279 (0.166–0.469)	<0.0001	0.267 (0.159–0.449)	<0.0001
55–59 years	0.425 (0.277–0.653)	<0.0001	0.425 (0.276–0.652)	<0.0001
60–64 years	0.555 (0.394–0.781)	0.0007	0.532 (0.377–0.749)	0.0003
65–69 years	1 (Ref.)	–	1 (Ref.)	–
70–74 years	1.035 (0.770–1.391)	0.8216	1.052 (0.782–1.414)	0.7383
75–79 years	1.573 (1.088–2.274)	0.0161	1.686 (1.165–2.441)	0.0056
80+ years	4.272 (2.836–6.436)	<0.0001	5.246 (3.468–7.936)	<0.0001

CI, confidence interval; Ref., reference. GOLD grades were defined by FEV1, irrespective of the FEV_1/FVC ratio.

classification. They found that the spirometric classification predicted mortality better than the A-D classification. A similar conclusion was drawn from a study of Athlin et al. [6] comprising 490 patients with up to 12 years of follow-up, in which mortality rates were 2.5, 5.5 and 7.8 times higher in grades 2–4, respectively, compared to grade 1. Differences in sex distribution (mostly female, compared to mostly male in our study) might explain the differences in hazard ratios compared to our study to some extent. Whittaker et al. [4] followed up on almost 340,000 COPD patients in England for 5.5 years on average and found a strong relationship between GOLD grade and mortality, with adjusted mortality rates being 1.5, 2.5, and 4.2 times higher in grades 2–4, respectively, compared to grade 1. Except for grade 4, in which we estimated even much higher HRs, those estimates were fairly similar. An explanation for the higher HR for grade 4 in our study might be that the spread between the healthiest and the sickest participants was probably larger, possibly because we also included never smokers. Our study, while smaller than the studies of Whittaker or Gedebjerg, followed patients effectively for up to 9 years, making it the largest study with such long mortality follow-up and stratification by GOLD grade.

Notably, men had a considerably higher mortality than women, by approximately one third. Lower mortality among females with COPD has been suggested also by previous studies [37,38], even though the presence of residual confounders might contribute to these differences [37]. For example, women with COPD tend to have fewer smoking pack-years than men [39], which is expected to have an effect on mortality (e.g., risk of cardiovascular disease). Some studies [40] that adjusted for pack-years of smoking did not find statistically significant differences in mortality by sex, whereas a strong difference persisted in other studies [41] and is also observed in the general population in Germany [42]. Although we reported mortality rates also stratified by smoking status, those numbers should be interpreted with caution because of potential measurement errors (recall bias) in smoking assessment and the lack of more detailed smoking assessment (i.e. pack-years).

Based on our analysis, we derived, age-, sex- and grade-specific mortality rates for COPD, including measures of uncertainty. These mortality rates are crucial input parameters for decision-analytic models, such as Markov models or microsimulation models, that aim to simulate the course of COPD in the population.

Strengths of our analysis include the large number of participants (N = 2701), all of whom were recruited from distinguished study centers all over Germany. Thereby, our study is not only the first study of COPD mortality in a German population. Its study population probably well represents COPD patients in Germany. Follow-up was comparably long (up to 9 years), with health assessments in reasonably short intervals of 18 months. This resulted in comparably precise mortality estimates and reduced variability in the model parameters. During each study visit, a wide range of relevant variables was assessed in structured interviews, such as number and severity of exacerbations and quality of life. Spirometry (used for GOLD staging) was quality-assured by following established guidelines. Finally, this analysis is the first to our knowledge which derived age-, sex- and grade-specific mortality parameters for Markov models based on a representative German cohort of COPD patients, using a parametric survival model.

Our study also has limitations. In some cases, FEV_1 (seemingly) improved between visits, possibly as a result of submaximal effort during the earlier spirometry but also because of natural variability of FEV_1. This diagnostic instability could lead to an underestimation of mortality for more advanced grades, because the group of (for example) grade 3 patients at baseline might comprise some cases who were in fact in grade 2 or even grade 1. Besides, Markov models themselves (for which the age- and stage-specific mortality rates were derived) have several limitations. This includes the Markov assumption ("no memory", i.e. probabilities for future events like stage transition or death only depend on the current state and not the path taken to reach it). That assumption also implies an assumed exponential distribution of parameters. Furthermore, Markov models are not well-suited for very large numbers of possible states due to the exponential growth of possible transitions ("state-space explosion").

Estimations of mortality could be enhanced in future studies in various ways. For example, potential differences and changes in treatment could not be taken into account. Adherence to guidelines has been suggested to be associated with better survival [43]. On the other hand, there are indications that COSYCONET patients more likely show a higher degree of treatment compared to recommendations than a lower degree, i.e., undertreatment [44,45]. Thus, this factor might not have

Table 3
1-year mortality (95 % CIs) by age group, sex, and GOLD grade, derived from an exponential survival model. Excluding the first and last year of follow-up.

Calculated 1-year mortality rates with 95 % confidence intervals				
Age group	GOLD 1	GOLD 2	GOLD 3	GOLD 4
Males				
<55	0.00393 (0.00050–0.00736)	0.00714 (0.00197–0.01231)	0.01461 (0.00454–0.02469)	0.04141 (0.01288–0.06994)
55–59	0.00558 (0.00151–0.00965)	0.01012 (0.00437–0.01588)	0.02069 (0.00925–0.03214)	0.05830 (0.02521–0.09139)
60–64	0.00918 (0.00375–0.01461)	0.01664 (0.01024–0.02304)	0.03389 (0.02092–0.04686)	0.09430 (0.05823–0.13036)
65–69	0.01787 (0.00842–0.02732)	0.03227 (0.02292–0.04161)	0.06518 (0.04770–0.08265)	0.17602 (0.11822–0.23382)
70–74	0.01934 (0.00930–0.02939)	0.03491 (0.02501–0.04481)	0.07042 (0.05122–0.08962)	0.18922 (0.12729–0.25115)
75–79	0.02988 (0.01309–0.04667)	0.05369 (0.03383–0.07355)	0.10721 (0.06828–0.14614)	0.27802 (0.16977–0.38627)
80+	0.07827 (0.03122–0.12531)	0.13779 (0.08251–0.19307)	0.26263 (0.16786–0.35741)	0.58322 (0.40278–0.76365)
Females				
<55	0.00271 (0.00033–0.00509)	0.00493 (0.00130–0.00856)	0.01010 (0.00297–0.01722)	0.02873 (0.00836–0.04910)
55–59	0.00385 (0.00095–0.00674)	0.00699 (0.00285–0.01112)	0.01431 (0.00597–0.02265)	0.04056 (0.01582–0.06530)
60–64	0.00634 (0.00251–0.01016)	0.01150 (0.00672–0.01627)	0.02349 (0.01386–0.03311)	0.06599 (0.03871–0.09327)
65–69	0.01235 (0.00565–0.01905)	0.02235 (0.01513–0.02957)	0.04540 (0.03163–0.05916)	0.12493 (0.07909–0.17078)
70–74	0.01337 (0.00599–0.02076)	0.02419 (0.01576–0.03263)	0.04909 (0.03261–0.06557)	0.13462 (0.08187–0.18737)
75–79	0.02069 (0.00856–0.03282)	0.03732 (0.02187–0.05278)	0.07519 (0.04442–0.10596)	0.20112 (0.11158–0.29066)
80+	0.05463 (0.01907–0.09019)	0.09714 (0.05086–0.14342)	0.18942 (0.10705–0.27180)	0.45298 (0.27185–0.63411)
Overall				
<55	0.00311 (0.00062–0.00560)	0.00570 (0.00175–0.00965)	0.01188 (0.00401–0.01974)	0.03456 (0.01160–0.05753)
55–59	0.00452 (0.00125–0.00778)	0.00828 (0.00364–0.01291)	0.01722 (0.00779–0.02666)	0.04986 (0.02204–0.07767)
60–64	0.00740 (0.00315–0.01166)	0.01356 (0.00810–0.01902)	0.02813 (0.01755–0.03871)	0.08056 (0.04982–0.11131)
65–69	0.01483 (0.00747–0.02219)	0.02706 (0.01906–0.03507)	0.05574 (0.04122–0.07025)	0.15534 (0.10545–0.20524)
70–74	0.01657 (0.00837–0.02477)	0.03022 (0.02177–0.03867)	0.06212 (0.04443–0.07982)	0.17205 (0.11516–0.22895)
75–79	0.02512 (0.01114–0.03910)	0.04566 (0.02891–0.06241)	0.09306 (0.05967–0.12646)	0.24991 (0.15314–0.34668)
80+	0.06999 (0.02920–0.11077)	0.12477 (0.07537–0.17417)	0.24312 (0.15248–0.33376)	0.55957 (0.38293–0.73621)

GOLD grades were defined by FEV1, irrespective of the FEV_1/FVC ratio.

played a role. Other factors, particularly those arising from specific characteristics of the German health care system, can probably only be addressed by international comparisons. In addition, in future analyses it should be explored to which extent, particularly at the margins of the observation period and high COPD grades, comorbidities had an impact by disproportionally raising mortality risk [46]. Even if the prevalence of comorbidities did not strongly depend on COPD grade, their effect on mortality could.

5. Conclusions

In summary, in this work we estimated age-, sex-, and grade-specific survival of COPD patients from Germany and used the results to derive corresponding mortality rates which are needed in order to update a Markov model of COPD progression. Such updated mortality parameters are particularly helpful for long-term predictions of treatment costs and effects in the German context. Notably, COPD grade, age, sex, and smoking status were all relevant predictors of mortality. The results provided in this analysis might also help to develop general prediction models on survival in COPD patients. Future studies could assess differences in mortality between COPD, PRISm, and pre-COPD in more detail, using large-scale population-based studies, as well as consider potential influences of medical treatment.

CRediT authorship contribution statement

Tobias Niedermaier: Writing – original draft, Visualization, Methodology, Formal analysis. **Peter Alter:** Writing – review & editing. **Rudolf Jörres:** Writing – review & editing. **Claus Vogelmeier:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Rolf Holle:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization.

Funding

This study was supported by the German Federal Ministry of Education and Research (BMBF) as part of the PerMed-COPD Consortium (grant number 01 EK2203C). The COSYCONET cohort was supported by the BMBF as part of the Competence Network Asthma and COPD (ASCONET, grant number 01 GI 0881) and performed in collaboration with the German Center for Lung Research (DZL, grant number 82DZLI05B2). It was furthermore supported by unrestricted grants from industrial partners. The funders had no role in the study design, interpretation, or writing of the manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Claus Vogelmeier reports financial support was provided by German Federal Ministry of Education and Research (BMBF). Claus Vogelmeier reports a relationship with German Ministry of Education and Science (BMBF), AstraZeneca, Boehringer Ingelheim, Grifols, GlaxoSmithKline, and Novartis that includes: funding grants. Claus Vogelmeier reports a relationship with Aerogen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Nuvaira that includes: consulting or advisory. Claus Vogelmeier reports a relationship with Aerogen, AstraZeneca, Boehringer Ingelheim. that includes: speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We are grateful to all COSYCONET study centers, especially to all study nurses and physicians, for their excellent and enduring work in data collection, as well as to all patients who were willing to participate in this study over an extended period of time. The data management and quality assurance support provided by CAPNETZ STIFTUNG is gratefully acknowledged.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2025.108280.

References

[1] Global Initiative for Chronic Obstructive Lung Disease I, Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, 2024, 2024 Report.

[2] Frauen sterben deutlich häufiger an Lungen- und Bronchialkrebs als vor 20 Jahren. https://www.destatis.de/DE/Presse/Pressemitteilungen/2022/05/PD22_N033_23.html.

[3] C.F. Vogelmeier, F.W. Friedrich, P. Timpel, N. Kossack, J. Diesing, M. Pignot, M. Abram, M. Halbach, Impact of COPD on mortality: an 8-year observational retrospective healthcare claims database cohort study, Respir. Med. 222 (2024) 107506.

[4] H. Whittaker, K.J. Rothnie, J.K. Quint, Cause-specific mortality in COPD subpopulations: a cohort study of 339 647 people in England, Thorax 79 (3) (2024) 202–208.

[5] A. Lenoir, H. Whittaker, A. Gayle, D. Jarvis, J.K. Quint, Mortality in non-exacerbating COPD: a longitudinal analysis of UK primary care data, Thorax 78 (9) (2023) 904–911.

[6] A. Athlin, M. Giezeman, M. Hasselgren, S. Montgomery, K. Lisspers, B. Stallberg, C. Janson, J. Sundh, Prediction of mortality using different COPD risk assessments - a 12-Year Follow-Up, Int. J. Chronic Obstr. Pulm. Dis. 16 (2021) 665–675.

[7] E. Garcia Castillo, Perez T. Alonso, J. Ancochea, M.T. Pastor Sanz, P. Almagro, P. Martinez-Camblor, M. Miravitlles, M. Rodriguez-Carballeira, A. Navarro, B. Lamprecht, et al., Mortality prediction in chronic obstructive pulmonary disease comparing the GOLD 2015 and GOLD 2019 staging: a pooled analysis of individual patient data, ERJ Open Res. 6 (4) (2020).

[8] L. Bhatta, L. Leivseth, X.M. Mai, A.H. Henriksen, D. Carslake, Y. Chen, A. Langhammer, B.M. Brumpton, GOLD classifications, COPD hospitalization, and all-cause mortality in chronic obstructive pulmonary disease: the HUNT study, Int. J. Chronic Obstr. Pulm. Dis. 15 (2020) 225–233.

[9] M. Plutinsky, K. Brat, M. Svoboda, J. Zatloukal, P. Popelkova, V. Koblizek, Prognostic accuracy of three COPD classification systems in relation to long-term mortality of COPD patients: a prospective multicenter study, Lung 197 (2) (2019) 173–179.

[10] R.N. Criner, W.W. Labaki, E.A. Regan, J.M. Bon, X. Soler, S.P. Bhatt, S. Murray, J. E. Hokanson, E.K. Silverman, J.D. Crapo, et al., Mortality and exacerbations by global initiative for chronic obstructive lung disease groups ABCD: 2011 versus 2017 in the COPDGene(R) cohort, Chronic .Obstr. Pulm. Dis. 6 (1) (2019) 64–73.

[11] A. Gedebjerg, S.K. Szepligeti, L.H. Wackerhausen, E. Horvath-Puho, R. Dahl, J. G. Hansen, H.T. Sorensen, M. Norgaard, P. Lange, R.W. Thomsen, Prediction of mortality in patients with chronic obstructive pulmonary disease with the new global initiative for chronic obstructive lung disease 2017 classification: a cohort study, Lancet Respir. Med. 6 (3) (2018) 204–212.

[12] R. Faner, G. Noell, J.R. Badia, A. Lopez-Giraldo, P. Bakke, E.K. Silverman, R. Tal-Singer, A. Agusti, Distribution, temporal stability and association with all-cause mortality of the 2017 GOLD groups in the ECLIPSE cohort, Respir. Med. 141 (2018) 14–19.

[13] M.Z. Han, T.R. Hsiue, S.H. Tsai, T.H. Huang, X.M. Liao, C.Z. Chen, Validation of the GOLD 2017 and new 16 subgroups (1A-4D) classifications in predicting exacerbation and mortality in COPD patients, Int. J. Chronic Obstr. Pulm. Dis. 13 (2018) 3425–3433.

[14] L. Bhatta, L. Leivseth, D. Carslake, A. Langhammer, X.M. Mai, Y. Chen, A. H. Henriksen, B.M. Brumpton, Comparison of pre- and post-bronchodilator lung function as predictors of mortality: the HUNT study, Respirology 25 (4) (2020) 401–409.

[15] C. Guo, T. Yu, L.Y. Chang, Y. Bo, Z. Yu, M.C.S. Wong, T. Tam, X.Q. Lao, Mortality risk attributable to classification of chronic obstructive pulmonary disease and reduced lung function: a 21-year longitudinal cohort study, Respir. Med. 184 (2021) 106471.

[16] D. He, Y. Sun, M. Gao, Q. Wu, Z. Cheng, J. Li, Y. Zhou, K. Ying, Y. Zhu, Different risks of mortality and longitudinal transition trajectories in new potential subtypes of the preserved ratio impaired spirometry: evidence from the English longitudinal study of aging, Front. Med. 8 (2021) 755855.

[17] R. Perez-Padilla, F.C. Wehrmeister, M.M. de Oca, M.V. Lopez, J.R. Jardim, A. Muino, G. Valdivia, AMB Menezes, Outcomes for symptomatic non-obstructed individuals and individuals with mild (GOLD stage 1) COPD in a population based cohort, Int. J. Chronic Obstr. Pulm. Dis. 13 (2018) 3549–3561.

[18] C. Selya-Hammer, Guix N. Gonzalez-Rojas, M. Baldwin, A. Ternouth, M. Miravitlles, M. Rutten-van Molken, L.M. Goosens, N. Buyukkaramikli, V. Acciai, Development of an enhanced health-economic model and cost-effectiveness analysis of tiotropium + olodaterol Respimat(R) fixed-dose combination for chronic obstructive pulmonary disease patients in Italy, Ther. Adv. Respir. Dis. 10 (5) (2016) 391–401.

[19] J.B. Soriano, B. Lamprecht, A.S. Ramirez, P. Martinez-Camblor, B. Kaiser, I. Alfageme, P. Almagro, C. Casanova, C. Esteban, J.J. Soler-Cataluna, et al., Mortality prediction in chronic obstructive pulmonary disease comparing the GOLD 2007 and 2011 staging systems: a pooled analysis of individual patient data, Lancet Respir. Med. 3 (6) (2015) 443–450.

[20] T. Mattila, T. Vasankari, M. Kanervisto, T. Laitinen, O. Impivaara, H. Rissanen, P. Knekt, P. Jousilahti, S. Saarelainen, P. Puukka, et al., Association between all-cause and cause-specific mortality and the GOLD stages 1-4: a 30-year follow-up among Finnish adults, Respir. Med. 109 (8) (2015) 1012–1018.

[21] P. Menn, R. Leidl, R. Holle, A lifetime Markov model for the economic evaluation of chronic obstructive pulmonary disease, Pharmacoeconomics 30 (9) (2012) 825–840.

[22] A. Karch, C. Vogelmeier, T. Welte, R. Bals, H.U. Kauczor, J. Biederer, J. Heinrich, H. Schulz, S. Glaser, R. Holle, et al., The German COPD cohort COSYCONET: aims, methods and descriptive analysis of the study population at baseline, Respir. Med. 114 (2016) 27–37.

[23] K. Kahnert, C. Fischer, P. Alter, F. Trudzinski, T. Welte, J. Behr, F. Herth, H. U. Kauczor, R. Bals, H. Watz, et al., [What have we learned from the German COPD cohort COSYCONET and where do we go from here?], Pneumologie 77 (2) (2023) 81–93.

[24] M.P. Swanney, M.R. Miller, Adopting universal lung function reference equations, Eur. Respir. J. 42 (4) (2013) 901–903.

[25] P.W. Jones, F.H. Quirk, C.M. Baveystock, P. Littlejohns, A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire, Am. Rev. Respir. Dis. 145 (6) (1992) 1321–1327.

[26] P.H. Quanjer, S. Stanojevic, T.J. Cole, X. Baur, G.L. Hall, B.H. Culver, P.L. Enright, J.L. Hankinson, M.S. Ip, J. Zheng, et al., Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations, Eur. Respir. J. 40 (6) (2012) 1324–1343.

[27] B. Mayerhofer, R.A. Jorres, J.I. Lutter, B. Waschki, D. Kauffmann-Guerrero, P. Alter, F.C. Trudzinski, F.J.F. Herth, R. Holle, J. Behr, et al., Deterioration and mortality risk of COPD patients not fitting into standard GOLD categories: results of the COSYCONET cohort, Respiration 100 (4) (2021) 308–317.

[28] R. Kaaks, E. Christodoulou, E. Motsch, V. Katzke, M.O. Wielputz, H.U. Kauczor, C. P. Heussel, M. Eichinger, S. Delorme, Lung function impairment in the German Lung Cancer Screening Intervention Study (LUSI): prevalence, symptoms, and associations with lung cancer risk, tumor histology and all-cause mortality, Transl. Lung Cancer Res. 11 (9) (2022) 1896–1911.

[29] A. Agusti, R. Hughes, E. Rapsomaki, B. Make, R. Del Olmo, A. Papi, D. Price, L. Benton, S. Franzen, J. Vestbo, et al., The many faces of COPD in real life: a longitudinal analysis of the NOVELTY cohort, ERJ Open Res. 10 (1) (2024).

[30] C.J. Cadham, H. Oh, M.K. Han, D. Mannino, S. Cook, R. Meza, D.T. Levy, L. M. Sanchez-Romero, The prevalence and mortality risks of PRISm and COPD in the United States from NHANES 2007-2012, Respir. Res. 25 (1) (2024) 208.

[31] W.W. Labaki, T. Gu, S. Murray, J.L. Curtis, J.M. Wells, S.P. Bhatt, J. Bon, A.A. Diaz, C.P. Hersh, E.S. Wan, et al., Causes of and clinical features associated with death in tobacco cigarette users by lung function impairment, Am. J. Respir. Crit. Care Med. 208 (4) (2023) 451–460.

[32] S.R.A. Wijnant, E. De Roos, M. Kavousi, B.H. Stricker, N. Terzikhan, L. Lahousse, G. G. Brusselle, Trajectory and mortality of preserved ratio impaired spirometry: the Rotterdam study, Eur. Respir. J. 55 (1) (2020).

[33] E.S. Wan, P. Balte, J.E. Schwartz, S.P. Bhatt, P.A. Cassano, D. Couper, M. L. Daviglus, M.T. Dransfield, S.A. Gharib, D.R. Jacobs Jr., et al., Association between preserved ratio impaired spirometry and clinical outcomes in US adults, JAMA 326 (22) (2021) 2287–2298.

[34] M. Ekberg-Aronsson, K. Pehrsson, J.A. Nilsson, P.M. Nilsson, C.G. Lofdahl, Mortality in GOLD stages of COPD and its dependence on symptoms of chronic bronchitis, Respir. Res. 6 (1) (2005) 98.

[35] D.M. Mannino, D.E. Doherty, A. Sonia Buist, Global Initiative on Obstructive Lung Disease (GOLD) classification of lung disease and mortality: findings from the Atherosclerosis Risk in Communities (ARIC) study, Respir. Med. 100 (1) (2006) 115–122.

[36] K. Stavem, L. Sandvik, J. Erikssen, Can global initiative for chronic obstructive lung disease stage 0 provide prognostic information on long-term mortality in men? Chest 130 (2) (2006) 318–325.

[37] B. Celli, J. Vestbo, C.R. Jenkins, P.W. Jones, G.T. Ferguson, P.M. Calverley, J. C. Yates, J.A. Anderson, L.R. Willits, R.A. Wise, et al., Sex differences in mortality and clinical expressions of patients with chronic obstructive pulmonary disease. The TORCH experience, Am. J. Respir. Crit. Care Med. 183 (3) (2011) 317–322.

[38] J.P. de Torres, C.G. Cote, M.V. Lopez, C. Casanova, O. Diaz, J.M. Marin, V. Pinto-Plata, M.M. de Oca, H. Nekach, L.J. Dordelly, et al., Sex differences in mortality in patients with COPD, Eur. Respir. J. 33 (3) (2009) 528–535.

[39] T.A. Perez, E.G. Castillo, J. Ancochea, M.T. Pastor Sanz, P. Almagro, P. Martinez-Camblor, M. Miravitlles, M. Rodriguez-Carballeira, A. Navarro, B. Lamprecht, et al., Sex differences between women and men with COPD: a new analysis of the 3CIA study, Respir. Med. 171 (2020) 106105.

[40] J.K. Krishnan, M. Rajan, S. Banerjee, S.G. Mallya, M.K. Han, D.M. Mannino, F. J. Martinez, M.M. Safford, Race and sex differences in mortality in individuals with chronic obstructive pulmonary disease, Ann Am Thorac. Soc. 19 (10) (2022) 1661–1668.

[41] N. Li, X. Li, M. Liu, Y. Wang, J. Wang, Sex differences in comorbidities and mortality risk among patients with chronic obstructive pulmonary disease: a study based on NHANES data, BMC Pulm. Med. 23 (1) (2023) 481.

[42] Gestorbene Destasis, Jahre Deutschland, Geschlecht, Altersjahre (Code 12613-0003), 2023.

[43] I. Sarc, T. Jeric, K. Ziherl, S. Suskovic, M. Kosnik, S.D. Anker, M. Lainscak, Adherence to treatment guidelines and long-term survival in hospitalized patients with chronic obstructive pulmonary disease, J. Eval. Clin. Pract. 17 (4) (2011) 737–743.

[44] J. Graf, R. Jörres, T. Lucke, D. Nowak, C. Vogelmeier, J. Ficker, Medikamentöse Therapie der COPD-Analyse der leitliniengerechten Verordnung in einer großen nationalen Kohorte (COSYCONET, Dtsch. Arztebl. 115 (2018) 599–605.
[45] J.I. Lutter, R.A. Jorres, F.C. Trudzinski, P. Alter, C. Kellerer, H. Watz, T. Welte, R. Bals, D. Kauffmann-Guerrero, J. Behr, et al., Treatment of COPD groups GOLD A and B with inhaled corticosteroids in the COSYCONET cohort - determinants and consequences, Int. J. Chronic Obstr. Pulm. Dis. 16 (2021) 987–998.
[46] P. Alter, T. Lucke, H. Watz, S. Andreas, K. Kahnert, F.C. Trudzinski, T. Speicher, S. Sohler, R. Bals, B. Waschki, et al., Cardiovascular predictors of mortality and exacerbations in patients with COPD, Sci. Rep. 12 (1) (2022) 21882.