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COPD

Prognostic Accuracy of Three COPD Classification Systems in Relation to Long-Term Mortality of COPD Patients: A Prospective Multicenter Study

Marek Plutinsky[1] · Kristian Brat[1] · Michal Svoboda[2] · Jaromir Zatloukal[3] · Patrice Popelkova[4] · Vladimir Koblizek[5]

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Abstract

Recent research showed group B patients express higher mortality compared to group C patients when GOLD A-D grouping is used. We aimed to compare the prognostic accuracy of three GOLD classification systems, I–IV ("pre-2011"), A-D ("2011–2016") and A-D ("2017–present") in relation to mortality, exacerbation risk, quality of life (QoL) assessment and specific treatments use in a real-life COPD cohort. We used the data of 720 patients from the Czech Multicenter Research Database of COPD. Four-year mortality and time-to-exacerbation using the GOLD "pre-2011", "2011–2016" and "2017–present" classification schemes were assessed. Moreover, distribution of specific treatments use and QoL measures were analyzed. The GOLD I-IV classification system showed gradual increase in 4-year mortality across the stages (GOLD II 18.8%, III 28.5%, IV 38.7%) ($p=0.001$). Using the A-D "2011–2016" classification scheme, group C patients had lower mortality (16.7%) than group B (18.7%) ($p=0.009$). The A-D "2017–present" classification showed higher mortality in group B (25.5%) compared to group C (20%) ($p=0.05$). For additional outcomes, the GOLD I–IV scheme showed highest match between the calculated 4-year exacerbation risk and QoL measures and GOLD stage/grouping. In terms of specific treatment distributions, various patterns for each GOLD classification system were observed with best match of GOLD "2017–present" system to the layout of GOLD groups and categories. We conclude the GOLD I–IV classification system had the highest accuracy related to mortality, QoL measures and exacerbation risk prediction, while the A-D "2017–present" scheme was most accurate within severity of symptoms prediction reflected also by more frequent specific treatments use.

Keywords COPD · GOLD classification · Prognosis · Mortality

Introduction

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification of chronic obstructive pulmonary disease (COPD) underwent notable evolution

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✉ Kristian Brat
kristian.brat@seznam.cz

Marek Plutinsky
plutha@live.com

Michal Svoboda
svoboda@biostatistika.cz

Jaromir Zatloukal
Jaromir.Zatloukal@fnol.cz

Patrice Popelkova
patrice.popelkova@fno.cz

Vladimir Koblizek
vladimir.koblizek@fnhk.cz

[1] Department of Respiratory Diseases, University Hospital Brno and Faculty of Medicine, Masaryk University, Jihlavska 20, 62500 Brno, Czech Republic

[2] Institute of Biostatistics and Analyses, Ltd., Brno, Czech Republic

[3] Pulmonary Department, University Hospital Olomouc and Faculty of Medicine, Palacky University, Olomouc, Czech Republic

[4] Pulmonary Department, University Hospital Ostrava, Ostrava, Czech Republic

[5] Pulmonary Department, University Hospital Hradec Kralove and Charles University, Hradec Kralove, Czech Republic

during the last decade. The 2017 GOLD Update on COPD diagnosis and treatment [1] introduced a new approach in disease classification where magnitude of symptoms and exacerbation history are the only factors relevant to COPD grouping and treatment recommendation. The pre-2011 GOLD classification was based solely on the value of Forced Expiratory Volume in 1 s (FEV_1), recognizing 4 different stages (I–IV) with gradual predictive power to predict long-term mortality [2–5]. Research data showed that the recent GOLD classification into groups A-D possesses accuracy of prognostic value, i.e., patients in group B express higher long-term mortality compared to group C patients [3, 6, 7]. However, the data are sparse and further evidence is warranted to assess the appropriateness of the current COPD classification system in relation to long-term mortality prediction.

Methods

The aim of our study was to compare the prognostic accuracy of three different GOLD classification systems, I-IV ("pre-2011"), A-D ("2011–2016") and A-D ("2017–present"), in relation to long-term all-cause mortality in a real-life COPD patient cohort. For this purpose, we used the data from the Czech Multicenter Research Database of Severe COPD (CMRD) (ClinicalTrials.gov identifier NCT01923051) that is a prospective, multicenter (14 centers), observational and non-interventional project focused on long-term mortality of COPD subjects [8]. Inclusion criteria were diagnosis of COPD, $FEV_1 < 60\%$, stable disease for at least 8 weeks and patient's written consent [8]. Patient enrolment was started in 2013 and finished in December 2016 gaining a total of 784 patients that have since been followed-up regularly in 6-month periods [8]. Kaplan–Meier survival analysis was performed to assess 4-year survival/mortality of patients in the CMRD cohort using the GOLD "pre-2011", "2011–2016" and "2017–present" disease classification systems. Differences in survival between the groups were tested by Log Rank test. The primary goal of the GOLD 2011 and 2017 updates was to adjust treatment to parameters accessory/different than FEV_1 (i.e., symptoms, quality of life and risk of exacerbations). In order to meet these re-defined outcomes, we further assessed the data from our cohort in relation to long-term exacerbation risk, quality of life measures and specific treatments according to the 3 different GOLD COPD classification schemes. The study has been approved by the institutional Ethics Committee of the University Hospital Brno. Date of approval: January 16th, 2013; University Hospital Brno project registration code: "CHOPN".

Results

Basic characteristics of the study cohort are presented in Table 1. Of the 784 patients, 64 patients had incomplete data and were excluded from the further analysis. 73.1% were men, mean age was 66.6 years, 79.2% were current or past smokers, mean body mass index (BMI) was 27.1. Mean FEV_1 in the cohort was 44.4% of predicted value, the patients experienced a mean of 1.2 exacerbation during the last 12 months. In the mortality analysis, application of the GOLD I–IV classification system (Fig. 1a) showed significant differences or, more exactly, a gradual increase in 4-year mortality across the stages (GOLD II 18.8%, GOLD III 28.5%, GOLD IV 38.7%) ($p = 0.001$). With the use of GOLD A-D "2011–2016" classification system (Fig. 1b), group D was the most populous category encompassing 69.3% of the patient cohort. 20.8% of the patients were classified group B. Importantly, group C patients had lower 4-year mortality (16.7%) than group B patients (18.7%) ($p = 0.009$). Group A patients had the lowest (14.3%) while group D the highest (30.1%) all-cause mortality. The use of the GOLD A-D "2017–present" classification (Fig. 1c) had two important consequences. First, group B became the most populous category with 380 patients (52.8%), while the portion of group D patients was reduced down to 37.4%. Secondly, and similarly to the results presented in mortality Fig. 1b, the 4-year mortality in group B patients (25.5%) was significantly higher than in group C (20%) ($p = 0.05$).

Figure 2a–c shows the comparison of time to first exacerbation according to the 3 classification schemes. The GOLD pre-2011 classification system showed gradual increase in calculated 4-year exacerbation risk from GOLD stage II (53.2%), followed by GOLD stage III (58.9%) to GOLD stage IV (75%). In the GOLD 2011–2016 system, exacerbation risk was lowest in category A (25.8%) and highest in stage D (63.2%). However, we observed higher exacerbation risk in category B (57.3%) compared to category C (36.5%). Similar results were observed for GOLD 2017–present classification system (29.5% group A, 55.3% group B, 42.1% group C and 72.2% group D). These results are in accordance with the observations obtained from the mortality analysis.

The distribution of clinical symptoms, quality of life measures and specific treatments across the three COPD GOLD classification approaches is presented in Supplementary Table 1 (for the GOLD "pre-2011" system), Supplementary Table 2 (for the GOLD "2011–2017" classification system) and Supplementary Table 3 (for the GOLD "2017–present" system). Our results showed significant prominence of bronchitic symptoms (cough and expectoration) in categories B and D (using the GOLD "2011–2017"

Table 1 Basic characteristics of the cohort ($n = 720$)

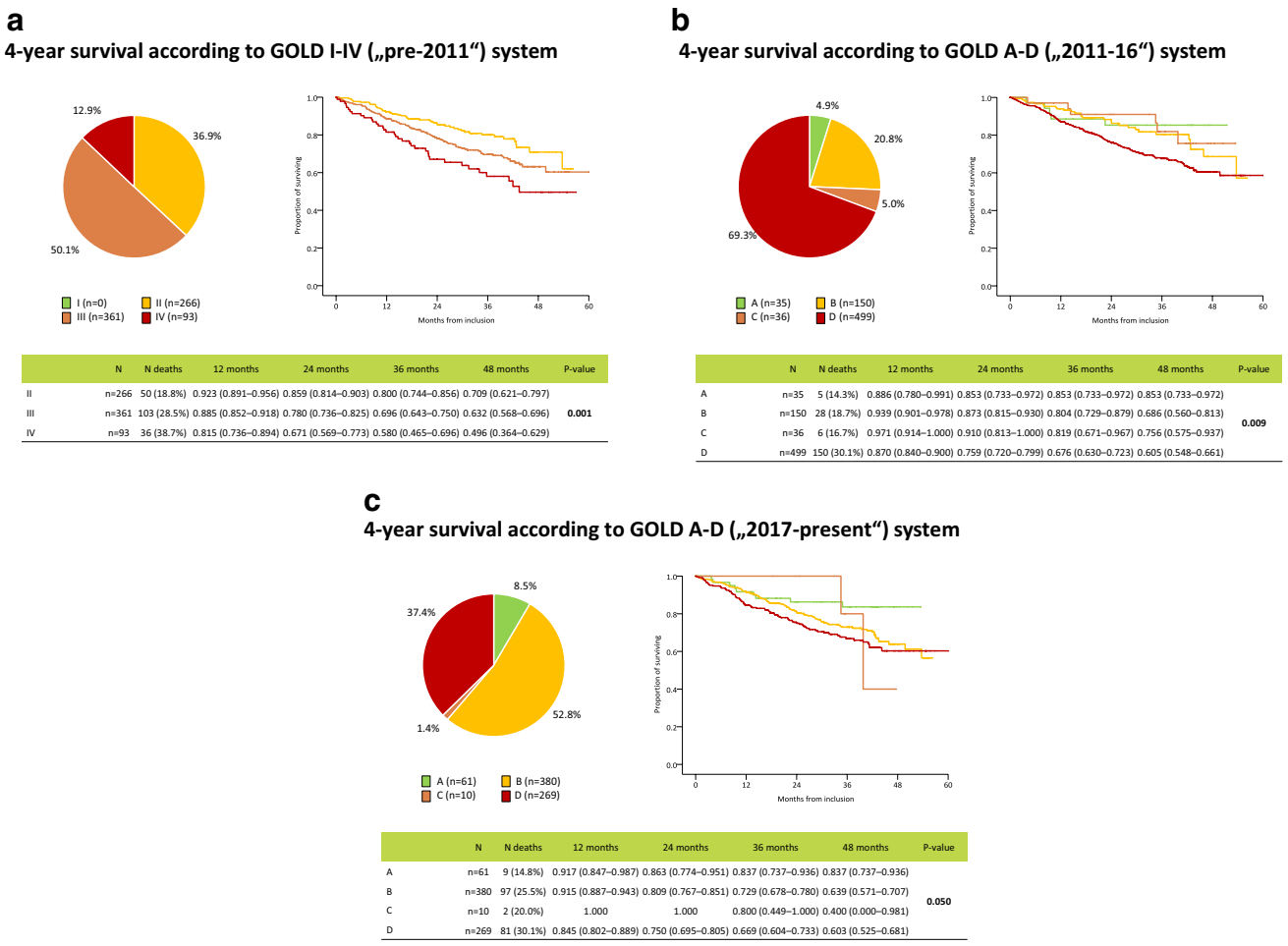
Demographic data	
Men	526 (73.1%)
Age at inclusion	$n = 720$; 66.6 (9.3); 67.0 (50.4; 81.1)
Age at COPD diagnosis	$n = 682$; 58.7 (10.9); 59.6 (39.8; 74.5)
BMI (kg/m^2)	$n = 720$; 27.1 (6.0); 26.6 (18.3; 37.4)
Smoking status	
Ex-smoker	500 (69.4%)
Non-smoker	70 (9.7%)
Smoker	150 (20.8%)
Symptoms	
Dyspnoea—mMRC score	
0	33 (4.6%)
1	137 (19.0%)
2	287 (39.9%)
3	148 (20.6%)
4	115 (16.0%)
CAT score	$n = 714$; 16.1 (7.8); 16.0 (4.0; 29.0)
Fatigue	336 (47.2%)
Cough	523 (72.6%)
Expectoration	422 (58.6%)
Purulent sputum	39 (5.4%)
Hemoptysis	37 (5.1%)
Atopy	84 (11.7%)
Asthma	72 (10.0%)
Exacerbation history- previous 12 months	
Treated at home	$n = 720$; 0.8 (1.4); 0.0 (0.0; 3.0)
> 0	296 (41.1%)
Requiring hospital care	$n = 720$; 0.4 (0.8); 0.0 (0.0; 2.0)
> 0	183 (25.4%)
Total	$n = 720$; 1.2 (1.7); 1.0 (0.0; 4.0)
> 0	380 (52.8%)
Pulmonary function tests	
FEV_1 (% PV)	$n = 720$; 44.4 (11.4); 45.6 (25.0; 59.8)
FVC (% PV)	$n = 720$; 70.0 (17.3); 69.2 (41.8; 100.7)
VCmax (% PV)	$n = 720$; 73.1 (17.4); 72.0 (47.0; 101.0)
FEV_1/FVC (%)	$n = 720$; 0.5 (0.1); 0.5 (0.3; 0.7)
FEV_1/VCmax (%)	$n = 720$; 0.5 (0.1); 0.5 (0.3; 0.7)
RV (% PV)	$n = 578$; 189.4 (59.0); 187.0 (108.0; 291.0)
TLC (% PV)	$n = 575$; 112.4 (25.8); 112.4 (74.0; 156.0)
RV/TLC (%)	$n = 538$; 66.8 (21.0); 64.0 (44.0; 109.0)
IC/TLC (%)	$n = 414$; 42.1 (24.6); 33.0 (17.0; 83.3)
TL_{CO} (% PV)	$n = 466$; 52.1 (21.9); 50.0 (23.0; 97.0)
K_{CO} (%)	$n = 434$; 67.3 (25.3); 65.5 (31.0; 111.0)
FeNO (ppb)	$n = 273$; 18.7 (19.0); 12.0 (3.0; 52.0)
6-MWD (m)	$n = 551$; 335.3 (131.1); 360.0 (110.0; 530.0)
GOLD classification	
GOLD pre-2011 ("I–IV")	
1	0 (0.0%)
2	266 (36.9%)
3	361 (50.1%)
4	93 (12.9%)
GOLD 2011–2016 ("A–D")	
A	35 (4.9%)
B	150 (20.8%)
C	36 (5.0%)
D	499 (69.3%)
GOLD 2017 ("A–D")	
A	61 (8.5%)
B	380 (52.8%)
C	10 (1.4%)
D	269 (37.4%)
Predictive indices	
BODE	$n = 551$; 4.2 (2.1); 4.0 (1.0; 8.0)
ADO	$n = 711$; 4.7 (1.6); 5.0 (2.0; 7.0)

Categorical variables are presented as absolute or relative frequencies

Continuous parameters are presented as valid N, mean (SD), median (5th; 95th percentile)

COPD chronic obstructive pulmonary disease, *BMI* body mass index; *kg* kilogram, m^2 square meter, *mMRC* modified Medical Research Council dyspnoea scale, *CAT* COPD Assessment Test, *FEV1* forced expiratory volume in 1 s, *% PV* percent of predicted value, *FVC* forced vital capacity, *VCmax* maximum vital capacity, *FEV1/FVC* forced expiratory volume in 1 s to forced vital capacity ratio; % percent, *RV* residual volume, *TLC* total lung capacity; *RV/TLC* residual volume to total lung capacity ratio, *IC/TLC* inspiratory capacity to total lung capacity ratio, *TLco* transfer factor for carbon monoxide, *KCO* carbon monoxide transfer coefficient, *FeNO* fractional exhaled nitric oxide, *ppb* parts per billion; *6-MWD* 6 min walking distance, *m* meter, *GOLD* the Global Initiative for Chronic Obstructive Lung Disease, *BODE* body mass index, airflow obstruction, dyspnoea, exercise, *ADO* age, dyspnoea, airflow obstruction

and "2017–present" classification approaches). In terms of QoL assessment, the GOLD "pre-2011" system had the most accurate concordance between the increasing SGRQ total score and the gradual increase in GOLD grade/category (i.e., from grade I to IV or from category A to D) (Supplementary Tables 1–3). With the use of the GOLD "2011–2017" and "2017–present" classification schemes, categories B and D had highest total SGRQ scores (compared to categories A and C) in our cohort. The assessment of treatment distributions in relation to GOLD stages and categories showed various patterns of specific treatments use for each GOLD classification system. However, the results for the GOLD "2017–present" system possibly best



	N	N deaths	12 months	24 months	36 months	48 months	P-value
II	n=266	50 (18.8%)	0.923 (0.891–0.956)	0.859 (0.814–0.903)	0.800 (0.744–0.856)	0.709 (0.621–0.797)	
III	n=361	103 (28.5%)	0.885 (0.852–0.918)	0.780 (0.736–0.825)	0.696 (0.643–0.750)	0.632 (0.568–0.696)	**0.001**
IV	n=93	36 (38.7%)	0.815 (0.736–0.894)	0.671 (0.569–0.773)	0.580 (0.465–0.696)	0.496 (0.364–0.629)	

	N	N deaths	12 months	24 months	36 months	48 months	P-value
A	n=35	5 (14.3%)	0.886 (0.780–0.991)	0.853 (0.733–0.972)	0.853 (0.733–0.972)	0.853 (0.733–0.972)	
B	n=150	28 (18.7%)	0.939 (0.901–0.978)	0.873 (0.815–0.930)	0.804 (0.729–0.879)	0.686 (0.560–0.813)	**0.009**
C	n=36	6 (16.7%)	0.971 (0.914–1.000)	0.910 (0.813–1.000)	0.819 (0.671–0.967)	0.756 (0.575–0.937)	
D	n=499	150 (30.1%)	0.870 (0.840–0.900)	0.759 (0.720–0.799)	0.676 (0.630–0.723)	0.605 (0.548–0.661)	

	N	N deaths	12 months	24 months	36 months	48 months	P-value
A	n=61	9 (14.8%)	0.917 (0.847–0.987)	0.863 (0.774–0.951)	0.837 (0.737–0.936)	0.837 (0.737–0.936)	
B	n=380	97 (25.5%)	0.915 (0.887–0.943)	0.809 (0.767–0.851)	0.729 (0.678–0.780)	0.639 (0.571–0.707)	**0.050**
C	n=10	2 (20.0%)	1.000	1.000	0.800 (0.449–1.000)	0.400 (0.000–0.981)	
D	n=269	81 (30.1%)	0.845 (0.802–0.889)	0.750 (0.695–0.805)	0.669 (0.604–0.733)	0.603 (0.525–0.681)	

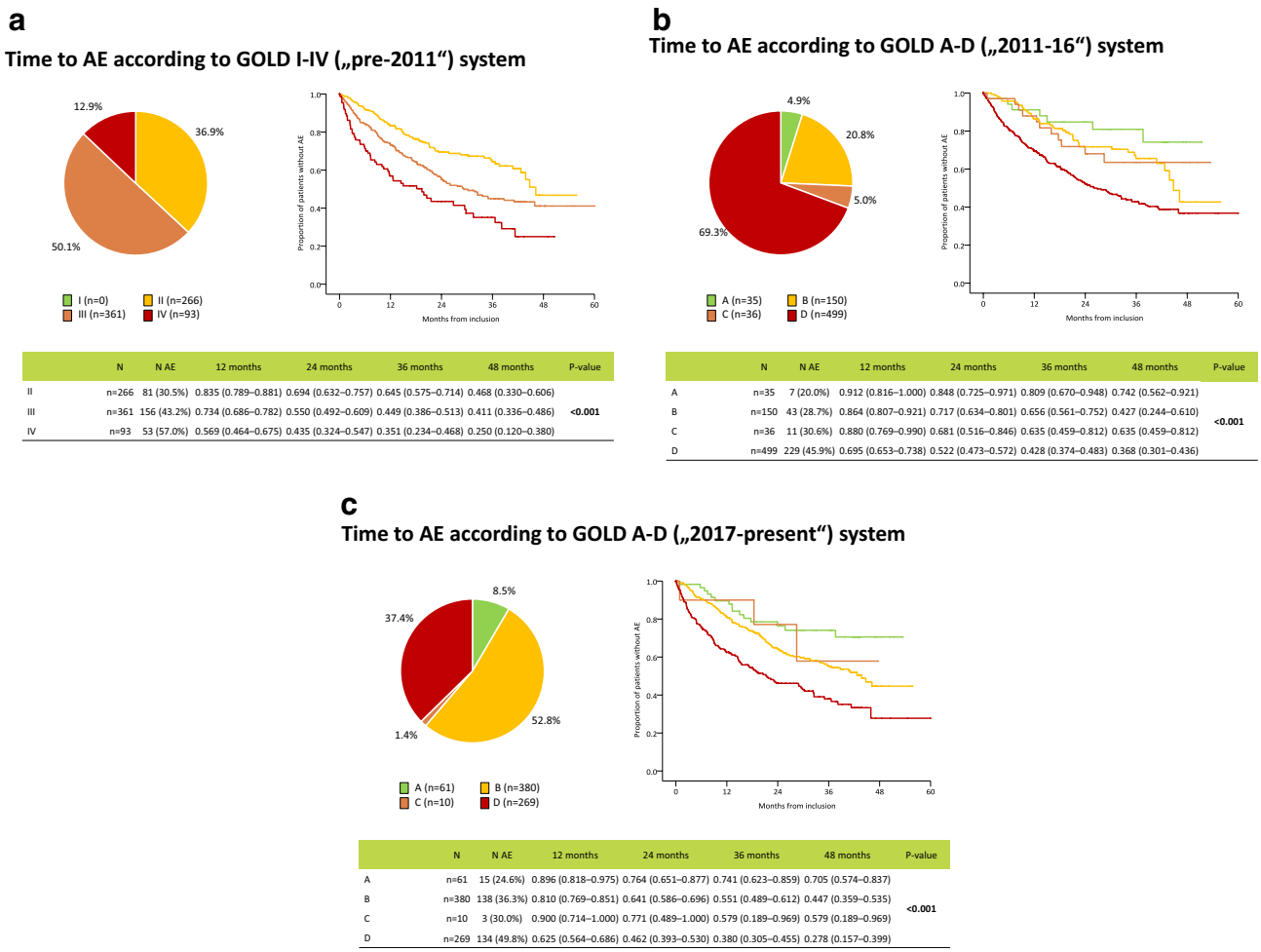
Fig. 1 **a** 4-year survival according to GOLD I-IV ("pre-2011") system, **b** 4-year survival according to GOLD A-D ("2011–2016") system, **c** 4-year survival according to GOLD A-D ("2017–present") system

matched the layout of GOLD categories since category D had the highest frequency of specific treatments use (reflecting the highest level of disease severity).

Discussion

The results of mortality analysis from the CMRD cohort are in good accordance with previous reports from large COPD patient cohorts. In the ECLIPSE and the Copenhagen study cohorts, mortality of COPD patients was significantly higher in group B than in group C (using the GOLD "2011–2016" classification) [3, 5, 9]. This phenomenon has been considered to be a consequence of higher comorbidity rates in COPD group B patient subpopulation [3]. This classification system had the advantage of better identification of COPD individuals with higher risk of exacerbation. However, due to the above-mentioned prognostic shortcoming in relation to mortality prediction, there has been a strong call for a revision of the GOLD guideline. Since 2017, the GOLD update of COPD classification (A-D "2017–present") has been introduced [1]. Recent studies have shown that a separate assessment of symptoms/exacerbation history and lung function resulted in major shifts of patients from groups C to A and D to B [6, 7]. In our study, we also observed major shift of patients from category D to group B. Moreover, we demonstrated that the expected improvement in prognostic accuracy of the GOLD "2017–present" guideline failed in terms of gradual (from A to D group) long-term mortality prediction—in our cohort, group B patients had higher 4-year mortality than group C patients. Accordingly, Cabrera Lopez et al. reported higher mortality in group B compared to group C patients during a similar follow-up period [7].

Above that, we learned that group B is currently the largest subcategory of COPD patients (52.7%) in populations of non-mild COPD subjects. Similar data were recently reported from the POPE study where the proportion of category B patients was 50.1% of the cohort [6, 10]. These data suggest that group B became the largest category of COPD patients. Group B patients, however,



	N	N AE	12 months	24 months	36 months	48 months	P-value
II	n=266	81 (30.5%)	0.835 (0.789–0.881)	0.694 (0.632–0.757)	0.645 (0.575–0.714)	0.468 (0.330–0.606)	
III	n=361	156 (43.2%)	0.734 (0.686–0.782)	0.550 (0.492–0.609)	0.449 (0.386–0.513)	0.411 (0.336–0.486)	**<0.001**
IV	n=93	53 (57.0%)	0.569 (0.464–0.675)	0.435 (0.324–0.547)	0.351 (0.234–0.468)	0.250 (0.120–0.380)	

	N	N AE	12 months	24 months	36 months	48 months	P-value
A	n=35	7 (20.0%)	0.912 (0.816–1.000)	0.848 (0.725–0.971)	0.809 (0.670–0.948)	0.742 (0.562–0.921)	
B	n=150	43 (28.7%)	0.864 (0.807–0.921)	0.717 (0.634–0.801)	0.656 (0.561–0.752)	0.427 (0.244–0.610)	**<0.001**
C	n=36	11 (30.6%)	0.880 (0.769–0.990)	0.681 (0.516–0.846)	0.635 (0.459–0.812)	0.635 (0.459–0.812)	
D	n=499	229 (45.9%)	0.695 (0.653–0.738)	0.522 (0.473–0.572)	0.428 (0.374–0.483)	0.368 (0.301–0.436)	

	N	N AE	12 months	24 months	36 months	48 months	P-value
A	n=61	15 (24.6%)	0.896 (0.818–0.975)	0.764 (0.651–0.877)	0.741 (0.623–0.859)	0.705 (0.574–0.837)	
B	n=380	138 (36.3%)	0.810 (0.769–0.851)	0.641 (0.586–0.696)	0.551 (0.489–0.612)	0.447 (0.359–0.535)	**<0.001**
C	n=10	3 (30.0%)	0.900 (0.714–1.000)	0.771 (0.489–1.000)	0.579 (0.189–0.969)	0.579 (0.189–0.969)	
D	n=269	134 (49.8%)	0.625 (0.564–0.686)	0.462 (0.393–0.530)	0.380 (0.305–0.455)	0.278 (0.157–0.399)	

Fig. 2 **a** Time to AE according to GOLD I-IV (“pre-2011”) system. **b** Time to AE according to GOLD A-D (“201–2016”) system. **c** Time to AE according to GOLD A-D (“2017–present”) system

are more symptomatic, and it is likely that a substantial portion of these patients may progress rapidly to stage D. Last but not least, it is probable that group B encompasses patient subpopulations with various risk of long-term mortality. As recently reported by our research group, COPD patients group B had significant differences in long-term outcome according to their respiratory parameters (i.e., chronic hypoxemia was a strong risk factor of increased long-term mortality) [11]. In contrast, Cabrera Lopez et al. reported group A was the most populous COPD patient category possibly reflecting regional differences in patient distribution across COPD A-D groups [7, 10]. In recent years, evidence for phenotyping of COPD is emerging not only due to the possibility of a more individualized pharmacological treatment of COPD patients but also for its potential to become an additional approach for long-term mortality prediction [12, 13]. Our results as well as other research data suggest that an update of COPD classification would be beneficial.

Quality of life (QoL) and dyspnoea measures regularly assessed in the CMRD cohort include the mMRC (modified Medical Research Council) dyspnoea scale, CAT (COPD Assessment Test) and the SGRQ (St. George´s Respiratory Questionnaire). The mMRC and CAT tests are both factors that determine the COPD category assignment within the GOLD “2011–2017” and “2017–present” classification schemes. To avoid a petitio principii, these measures were excluded from a separate QoL analysis in our study. On the other hand, the SGRQ data were not available for all patients of the CMRD cohort since this parameter was not mandatory to complete at patient enrolment.

The use of the recommended bronchodilator treatment according to GOLD categories has been assessed in previous studies [6]. Thus, we analyzed only the distribution of specific treatments use (inhaled corticosteroids (ICS), roflumilast, antibiotics (azithromycin) and mucolytic agents (erdosteine, N-acetylcysteine)) across each GOLD classification scheme. In our study, we observed that the use

of specific medications was most frequent in GOLD category D (according to the "2017–present" GOLD guideline). GOLD group D now appears to be a well-defined category encompassing the most severe COPD patients not only related to symptoms burden and QoL, but also figures as the subgroup of COPD patients with the highest risk of long-term all-cause mortality [11].

The accordance between the patterns of long-term mortality risk and the time to first exacerbation for all 3 classification schemes observed in our study was most likely driven by exacerbations proper. This is in agreement with previously published research where COPD exacerbations count for one of the most important prognosis-defining and mortality-related factors [14–16].

The most important limitation of this study is that the CMRD cohort is composed solely of non-mild COPD subjects ($FEV_1 < 60\%$). On the other hand, the exclusion of patients with mild bronchial obstruction prevents from the enrolment of patients with hypothetically reversible bronchial obstruction (from a long-term perspective). Second, the cohort included 73% of men that might introduce a gender bias. The major strengths of the presented research are the robustness, the complexity and the prospective character of the data that were gained from 14 participating centers in the Czech Republic. To our best knowledge, this is the first study that evaluated and compared face-to-face the specific features and characters of the 3 GOLD classification schemes in their complexity.

We conclude that the GOLD I-IV "pre-2011" classification system had the highest accuracy related to prediction of long-term all-cause mortality, exacerbation risk and QoL assessment when compared to the GOLD A-D "2011–2016" and A-D "2017–present" systems. Currently, group B represents the largest subcategory of COPD patients in real-life cohorts. In terms of symptoms prominence, the GOLD A-D "2017–present" classification scheme appears to have the highest accuracy that is reflected also in specific treatments use within our study cohort.

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Compliance with Ethical Standards

Conflict of interest The authors declare no conflicts of interest in relation to the presented work.

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