Mortality prediction in chronic obstructive pulmonary disease comparing GOLD2015 and GOLD2019 staging

García Castillo, Elena; Alonso Pérez, Tamara; Ancochea, Julio; Pastor-Sanz, Teresa María; Almagro, Pere; Martínez-Camblor, Pablo; Rodríguez-Carballeira, Monica; Navarro, Annie; Lamprecht, Bernd; Sofia Ramírez, Ana; Kaiser, Bernhard; Alfageme, Inmaculada; Casanova, Ciro; Esteban, Cristóbal; Soler Cataluña, Juan José; Celli, Bartolome; Marin, Jose Maria; Ter Riet, Gerben; Sobradillo, Patricia; Lange, Peter

DOI: 10.1183/13993003.congress-2020.966

License: Other (please provide link to licence statement)

Citation for published version (Harvard):

Link to publication on Research at Birmingham portal

Publisher Rights Statement:
This is an author-submitted, peer-reviewed version of a manuscript that has been accepted for publication in the European Respiratory Journal, prior to copy-editing, formatting and typesetting. This version of the manuscript may not be duplicated or reproduced without prior permission from the copyright owner, the European Respiratory Society. The publisher is not responsible or liable for any errors or omissions in this version of the manuscript or in any version derived from it by any other parties. The final, copy-edited, published article, which is the version of record, is available without a subscription 18 months after the date of issue publication.

General rights
Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

• Users may freely distribute the URL that is used to identify this publication.
• Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
• Users may use extracts from the document in line with the concept of ‘fair dealing’ under the Copyright, Designs and Patents Act 1988 (?)
• Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy
While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Download date: 15. Sep. 2023
Mortality prediction in chronic obstructive pulmonary disease comparing GOLD2015 and GOLD2019 staging: a pooled analysis of individual patient data

Journal: ERJ Open Research

Manuscript ID ERJOR-00253-2020.R1

Manuscript Type: Original Article

Date Submitted by the Author: 30-Jul-2020

Complete List of Authors:
García Castillo, Elena; Hospital Universitario de la Princesa, Pulmonology Alonso Pérez, Tamara; Hospital Universitario de la Princesa, Pulmonology department
Ancochea, Julio; Universidad Autonoma de Madrid, Servicio de Neumología, Hospital La Princesa
Pastor-Sanz, María Teresa; Instituto de Investigación Hospital Universitario de la Princesa (IISP), Universidad Autónoma de Madrid, Universidad Autónoma de Madrid
Almagro, Pere; University Hospital Mutua de Terrassa, Internal Medicine
Martinez-Cambor, Pablo; Dartmouth College Geisel School of Medicine, The Dartmouth Institute for Health Policy and Clinical Practice
Miravitlles, Marc; Hospital Universitari Vall d’Hebron, Pneumology Department
Rodriguez-Carballeira, Monica; University Hospital Mutua de Terrassa, Internal Medicine
Navarro, Annie; Hospital Mutua Terrassa. University of Barcelona., Pneumology
Lamprecht, Bernd; Kepler University Hospital, Department of Pulmonary Medicine; Johannes-Kepler-University, Faculty of Medicine
Ramirez Garcia-Luna, Ana Sofia
Kaiser, Bernhard; Paracelsus Medical University, Pulmonary Medicine Alfageme, Inmaculada; Unidad de Gestión Clínica de Neumología, Hospital Universitario Virgen de Valme, Universidad de Sevilla, Sevilla
Casanova, Ciro; Unidad de Investigación , Respiratory Medicine
ESTEBAN, CRISTÓBAL; GALDAKAO-USANSOLO HOSPITAL, PNEUMOLOGY
Soler Cataluña, Juan José; Hospital Arnau de Vilanova, Servicio de Neumología
de Torres, JP; Servicio de Neumología, Clínica Universitaria de Navarra, Pamplona, España
Celli, Bartolome ; Brigham and Women’s Hospital, Pulmonary and Critical Care Division
Marin, Jose Maria; Hospital Universitario Miguel Servet, Respiratory Service
ter Riet, Gerben; Department of General Practice , Academic Medical Center,
Sobradillo, Patricia

https://mc.manuscriptcentral.com/erjor
Lange, Peter; Herlev Hospital, ; Copenhagen University, Department of Public Health
Garcia Aymerich, Judith; Instituto de Salud Global Barcelona, Campus Mar; Universitat Pompeu Fabra,
Antó, Josep Maria; Instituto de Salud Global Barcelona,
Turner, Alice M; 23. Institute of Applied Health Research, University of Birmingham , Edgbaston , UK
Han, MeiLan; University of Michigan, Internal Medicine
Langhammer, Arnulf; Norwegian University of Science and Technology, HUNT Research Centre, Department of Public Health and General Practice
Vikjord, Sigrid Anna; Norwegian University of Science and Technology, Department of Public Health and Nursing
Sternberg, Alice; Johns Hopkins University Bloomberg School of Public Health
Leivseth, Linda; Centre Northern Norway Regional Health Authority, Centre for Clinical Documentation and Evaluation
Bakke, Per ; University of Catania, Department of Clinical and Experimental Medicine
Johannessen, Ane; Department of Global Public Health and Primary Care, University of Bergen, Bergen, Bergen, Norway
Oga, Toru; Graduate School of Medicine, Kyoto University, Respiratory Care and Sleep Control Medicine
Cosio, Borja; Hospital Universitario Son Espases, Respiratory Medicine-IDTISBa; CIBERES, COPD CRP
Echazarreta, Andrés; 32. Servicio de Neumología, Hospital San Juan de Dios de La Plata, Buenos Aires, Argentina
Roche, Nicolas; Respiratory Medicine, Cochin Hospital APHP, University Paris Descartes, Paris, France
Burgel, Pierre Regis; Cochin Hospital, APHP, Pulmonary Department and Adult CF Centre
Sin, Don; University of British Columbia and The Providence Heart and Lung Institute and the James Hogg Research Laboratories, St. Paul’s Hospital, Department of Medicine (Division of Respirology)
Puhan, Milo; 36. Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland
Lopez-Campos, Jose Luis; Hospital Universitario Virgen del Rocio, Unidad Médico-Quirúrgica de Enfermedades Respiratorias; CIBER de Enfermedades Respiratorias (CIBERES),
Carrasco, Laura; Hospital Universitario Virgen del Rocio, Unidad Médico-Quirúrgica de Enfermedades Respiratorias
Soriano, Joan B; Instituto de Investigación Hospital Universitario de la Princesa (IISP), Universidad Autónoma de Madrid, Universidad Autónoma de Madrid;

Key Words: COPD, mortality, Survival analysis
ERJOR-00253-2020

The full comments of the reviewers are as follows:

Reviewer: 1

Comments to the Author
Castillo et al. included a large sample size to predict the mortality in GOLD 2015 vs 2019. Some major limitations are mentioned in the discussion part. Some important questions occurred while reading the manuscript:

1. Was the study registered in Clinical Trials
   RESPONSE #1: Negative. The 3CIA initiative is a compilation of individually published COPD clinical cohorts which started in 2015 [Lancet Respir Med. 2015 PMID: 25995071]. In retrospect, it was the internationalization of the Spanish-based COCOMICS study, which started in 2011 and produced its first publication in 2013 [Eur Respir J. 2013 PMID: 23222874]. At that time, it was not a journal requirement to register observational studies at https://clinicaltrials.gov or elsewhere. However, for the record most of the individual COPD clinical cohorts are/have been registered.

2. How many patients received oxygen (LTOT)?
   RESPONSE #2: As suggested, we attach the data on the number and percentage of patients receiving long term oxygen therapy.

3. Can you provide pCO2 values in table 1.
   RESPONSE #3: Regrettably, our protocol requested a set of core variables that did not include pCO2 or any blood gases.

4. Do you have data for emphysema or hyperinflation since this was described as predictors for mortality (Budweiser et al. Journal of COPD Vol 11 2014)
   RESPONSE #4: Similar to RESPONSE #3, same applied to CT-scan for the entire pooled 3CIA database.

5. Is an inclusion bias possible since the inclusion of the centers seemed to be pretty different - please comment and ad some data if the inclusion is driven by a small number of centers.
   RESPONSE #5: We kindly differ with Reviewer 1, as the small number of centres (22 cohorts of eleven countries) might be a restriction of representativity, but not a bias (neither selection, information nor confounding). However, the following text has been included in Limitations, page 13:

   “… or a primary care population. Indeed, the 22 cohorts from eleven countries in 3CIA within our initiative are only a sample representing the estimated 300 million COPD patients worldwide [new ref: Lancet Respir Med. 2020 Jun;8(6):585-596. doi: 10.1016/S2213-2600(20)30105-3. PMID: 32526187]. Finally, the recruitment timeframe was long (10 years), so evolving treatment recommendations might influence results.”

6. How did you define exacerbation - was the same definition used for every center? (page 7 line 6)
   RESPONSE #6: Thanks for allowing us to highlight this most critical issue. We have identified a related, recent ERJ Open Res paper, and the following paragraph is now included in Discussion, page 10:

7. Since the comorbidities are missing mortality is a difficult approach from my perspective- please comment.

**RESPONSE #7**: In our study, we showed the number and percentage of patients with COPD who present comorbidities such as hypertension, diabetes mellitus, cardiac disease or asthma.

8. What is the clinical impact of the displayed data? Would the data influence your clinical decisions?

**RESPONSE #8**: Candidly, see our paragraphs on research relevance in pages 8 and 9. Indeed, the implication of progressively milder disease classifications for the treatment choices clinicians make in real life practice guided by GOLD is not yet clear, but will be important to monitor.

9. What is your suggestion to define a more precise prediction scale for mortality.

**RESPONSE #9**: The following text and references has been included in Discussion, page 13:

“…Ours should be considered a constructive exercise and a critical appraisal of the last two GOLD iterations defining COPD. Within 3CIA, we have already suggested several proposals for future COPD staging and grading classifications, by applying more evidence-based thresholds of evidence-based variables. [New references.]”

New references:


Please add some thoughts in the discussion.

RESPONSE #10: We have significantly expanded our Discussion section with the clarifications previously exposed and 8 new references.

Associate Editor: Andreas, Stefan
Comments to the Author:
The mortality data on GOLD 2015 vs 2019 classification are well presented in a large, international cohort. Please add in table 4: Accuracy for predicting mortality…

RESPONSE #11: As requested, we modify the table 4 title.
Mortality prediction in chronic obstructive pulmonary disease comparing the GOLD 2015 and GOLD 2019 staging: a pooled analysis of individual patient data

Elena García Castillo1 *, Tamara Alonso Pérez1 *, Julio Ancochea1, Maria Teresa Pastor Sanz1, Pere Almagro2, Pablo Martínez-Camblor3, Marc Miravitlles4, Mónica Rodríguez-Carballeira5, Annie Navarro6, Bernd Lamprecht7, Ana S Ramirez-García Luna8, Bernhard Kaiser9, Inmaculada Alfageme10, Ciro Casanova11, Cristóbal Esteban12, Juan J Soler-Cataluña13, Juan P de-Torres14, Bartolomé R Celli15, Jose M Marín16, Gerben ter Riet17, Patricia Sobradillo18, Peter Lange19, Judith García-Aymerich20,21,22, Josep M Anto20,21,22, Alice M Turner23, MeiLan K Han24, Arnulf Langhammer25, Sigrid Anna Aalberg Vikjord25, Alice Sternberg26, Linda Leivseth27, Per Bakke28, Ane Johannessen29, Toru Oga30, Borja Cosío31, Andrés Echazarreta32, Nicolás Roche33, Pierre-Régis Burget34, Don D Sin, Milo34,35, Milo A Puhan36, Jose Luis López Campos37, Laura Carrasco38, Joan B Soriano39 & for the 3CIA collaboration.

* Shared first authors

Author information:

1. Pneumology Department, Hospital Universitario de la Princesa. Instituto de Investigación Hospital Universitario de la Princesa (IISPr), Universidad Autónoma de Madrid, Madrid, Spain.
2. Multimorbidity Patients Unit, Internal Medicine Dept, University Hospital Mutua de Terrassa, University of Barcelona, Barcelona, Spain.
3. Geisel School of Medicine at Dartmouth, Hanover, NH, USA.
4. Pneumology Department, Hospital Universitary Vall d’Hebron, CIBER de Enfermedades Respiratorias (CIBERES), Barcelona, Spain.
5. Multimorbidity Patients Unit, Internal Medicine, Hospital Universitari Mutua de Terrassa, Universitat de Barcelona, Barcelona, Spain.
6. Pneumology Service, Hospital Universitari Mutua Terrassa, Barcelona, Spain.
7. Department of Pulmonary Medicine, Kepler-University-Hospital. Faculty of Medicine, Johannes-Kepler-University Linz, Austria.
8. Facultad de Medicina, Universidad Autónoma de San Luis Potosí, San Luis Potosí, Mexico.
9. Department of Pulmonary Medicine, Paracelsus Medical University Hospital, Salzburg, Austria.
11. Hospital Universitario Nuestra Señora de La Candelaria, Universidad de La Laguna, Tenerife, Spain.
15. Pulmonary and Critical Care Medicine, Harvard University, Brigham and Women's Hospital, Boston, MA, USA.
16. Hospital Universitario Miguel Servet, Zaragoza, and CIBER de Enfermedades Respiratorias (CIBERES), Spain.
17. Department of General Practice, Academic Medical Center, University of Amsterdam (AMC), Amsterdam, The Netherlands.
18. Hospital Universitario Araba, Sede Txagorritxu, Vitoria, Spain for Universtary Hospital of Cruces in Barakaldo, Spain.
19. Section of Social Medicine, Department of Public Health, Copenhagen University, Copenhagen City Heart Study, Frederiksberg Hospital, Frederiksberg, Copenhagen, Denmark.
20. Global, Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain.
21. Department of Experimental and Health Sciences, Universitat Pompeu Fabra (UPF), Barcelona, Spain.
22. CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain.
23. Institute of Applied Health Research, University of Birmingham, Edgbaston, UK.
24. Internal Medicine, Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, MI, USA.
25. Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Trondheim, Norway.
26. Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA.
27. Centre for Clinical Documentation and Evaluation, Northern Norway Regional Health Authority, Tromso, Norway.
29. Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway.
30. Department of Respiratory Care and Sleep Control Medicine, Kyoto University, Kyoto, Japan.
31. Department of Respiratory Medicine, Hospital Son Espases-IdISPa, Ciberes, Mallorca, Spain.
32. Servicio de Neumonología, Hospital San Juan de Dios de La Plata, Buenos Aires, Argentina.
33. Respiratory Medicine, Cochin Hospital APHP, University Paris Descartes, Paris, France.
34. James Hogg Research Centre, University of British Columbia, Vancouver, BC, Canada.
35. Division of Respiratory Medicine, Department of Medicine, St Paul's Hospital, Vancouver, BC, Canada.
36. Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland.
37. Pulmonology Department. Hospital Universitario Virgen del Rocio, Sevilla, España.
38. Pulmonology Department. Hospital Universitario Virgen del Rocio, Sevilla, España.
39. Instituto de Investigación Hospital Universitario de la Princesa (IISP), Universidad Autónoma de Madrid, Madrid, Spain

**Address for correspondence:**

Dr. Joan B Soriano

Hospital Universitario de la Princesa, Diego de León 62, Neumología 6ª planta, 28006-Madrid, Spain

Email: jbsoriano2@gmail.com

Cellular: +34 618 86 77 69

**File information:**

Date: July, 2020

Word count: 2,838 words

References: 39 references

Illustrations: 4 tables and 4 figures

Keywords: COPD, mortality, survival
Mortality prediction in chronic obstructive pulmonary disease comparing the GOLD 2015 and GOLD 2019 staging: a pooled analysis of individual patient data

Abstract

In 2019, The Global Initiative for Chronic Obstructive Lung Disease (GOLD) modified the grading system for patients with chronic obstructive pulmonary disease (COPD) creating 16 subgroups (1A–4D). As part of the COPD Cohorts Collaborative International Assessment (3CIA) initiative, we aim to compare mortality prediction of 2015 and 2019 COPD GOLD staging systems.

We studied 17,139 COPD patients from the 3CIA study, selecting those with complete data. Patients were classified by the 2015 and 2019 GOLD ABCD systems and we compared the predictive ability for 5-year mortality of both classifications.

17,139 patients with COPD were enrolled in 22 cohorts of 11 countries between 2003 to 2017; 8,823 of them had complete data and were analyzed. Mean age was 63.9 years (SD 9.8) and 62.9% were male. GOLD 2019 classified the patients in milder degrees of COPD. For both classifications, group D had higher mortality. Five-year mortality did not differ between groups B and C in GOLD 2015; in GOLD 2019, mortality was greater for group B than C. Patients classified as group A and B had better sensitivity and positive predictive value with GOLD 2019 classification than GOLD 2015. GOLD 2015 had better sensitivity for group C and D than GOLD 2019. The AUC for 5-year mortality were only 0.67 (95% CI 0.66–0.68) for GOLD 2015 and 0.65 (95% CI 0.63–0.66) for GOLD 2019.

The new GOLD 2019 classification does not predict mortality better than the previous GOLD 2015 system.

Take Home message:

GOLD 2019 staging system created 16 subgroups
GOLD 2015 and GOLD 2019 are not strong predictors of mortality and don’t have sufficient discriminatory power to be used as a tool for risk classification of mortality in patients with COPD.
Chronic obstructive pulmonary disease (COPD) is a common cause of morbidity and mortality in the world. COPD affects approximately 328 million people worldwide, and COPD related deaths amount to 4 million deaths every year[1]. Assessment of disease severity is essential to predict prognosis and to standardize treatment regimes. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) document is the most widely used treatment guide for the staging and management of COPD. The GOLD grading system for COPD has significantly evolved since first publication in 2001 to the current version in 2019. Initially, in the GOLD 2007 classification, only post-bronchodilator airflow limitation based on spirometry forced expiratory volume in 1 second (FEV₁) was used to grade the severity of COPD[2]. Later on, some criticism arose on this grading score because it relied only upon FEV₁ which is not a good predictor of dyspnoea, quality of life or exercise tolerance. Further, other important variables to evaluate prognosis in COPD, such as sub-phenotypes, exacerbations, dyspnoea severity or comorbidities have been proposed, among others. Therefore, GOLD 2011 proposed a classification system of four groups, ABCD, combining FEV₁ and two clinical parameters: history of exacerbations and respiratory symptoms measured by the modified Medical Research Council (mMRC) dyspnoea score, or the COPD Assessment Test score (CAT) [3]. The 2011 ABCD classification was considered an improvement in the management of patients with COPD, providing an opportunity to further guide the individualized care of these patients. GOLD 2011 predicted future exacerbations better than GOLD 2007 but there was no difference in mortality predictions or respiratory outcomes [4-7]. In 2015 an updated report was published with the same measurement parameters (FEV₁, dyspnoea and exacerbations) than 2011 classification[8].

The latest GOLD update, published in 2019 uses a composite of spirometry, symptoms and exacerbations, but importantly separating the spirometric 1-4 staging from the ABCD groups[9]. This separation is relevant because it is known there are differences in the rate of exacerbations for the most severe COPD patients, depending on whether the risk is based on pulmonary function tests, on the history of exacerbations or both[10]. All these classifications were initially designed not to assess prognosis, but to aid clinicians in creating optimal treatment
regimes for patients. Thus, the prognostic ability of GOLD 2019 compared to previous classifications is largely unknown, with only a few published studies\(^{11,12}\). To address this issue, we used pooled data from 17,139 patients of 22 COPD cohorts and eleven countries and compared the prognostic capacity of the 2019 versus 2015 GOLD staging classifications to predict mortality.

**Methods**

**Study population**

In this international study, we assessed 17,139 patients from the COPD Cohorts Collaborative International Assessment (3CIA) initiative. All were prospective cohorts that recruited patients within the period 1999 to 2017, except one of them that was a population based cohort. All patients had a definition of COPD characterized by spirometry, that is post-bronchodilator FEV\(_1\) to forced vital capacity ratio (FVC) ratio less than 0.7 and a clinical diagnosis of COPD. Spirometry was performed using the standards provided by the American Thoracic Society and European Respiratory Society\(^{13}\). The primary investigators of each of the participating 3CIA cohorts provided individual patient's data for pooled analysis. We obtained a minimum individual dataset including the vital status (up to death, right truncation or 2017), age, sex, smoking status, pre-bronchodilator and post-bronchodilator FEV\(_1\) and FVC and dyspnoea measured with the modified mMRC, among others\(^{14}\). Only in a number of 3CIA cohorts were data of number of exacerbations in the previous year available. For the current study, we selected exclusively those cohorts in which the number of exacerbations in the previous year were available in the database, since this variable is required to calculate the GOLD 2015 and 2019 grading systems. Fifteen out of a total of 22 cohorts contained data on history of exacerbations, so that the final number of patients available to be classified according to GOLD 2015 and GOLD 2019 was 8,823. Symptoms were assessed using the mMRC dyspnoea scale. To determine the risk descriptor in the 2015 grouping system, we used exacerbations history and GOLD spirometry stages. The combination of symptoms (mMRC) and the worse risk descriptor (spirometry or exacerbation history) were used to classify patients by GOLD 2015 system. Participants were
classified using the GOLD 2019 system into four grades (1-4) based on postbronchodilator FEV₁ percentage of prediction as stage 1 (FEV₁ ≥ 80), stage 2 (FEV₁ 79-50), stage 3 (FEV₁ 30-49) and stage 4 (FEV₁ < 30). Groups ABCD were defined by self-reported severity of dyspnea (mMRC) and number of exacerbations in the previous year.

All participants provided informed written consent, and each study was conducted with the formal approval of the local ethics institutional committees following the principles of the Declaration of Helsinki.

Outcomes

The primary outcome was the prediction ability of all-cause mortality in the individuals by the two GOLD systems.

Statistical analysis

The 3CIA database manager quality-controlled all data centrally and created a clean database with a data dictionary. All implausible or missing variables were queried with the original study investigators, and datum were removed from the central database if errors could not be corrected. Because the cohorts had different follow-up times, patients were right-censored at five years of follow-up.

Descriptive statistics used mean and standard deviation for continuous variables and the number of cases and percentages for categorical variables. Comparisons between groups were performed with the Chi²-test for categorical variables and the T-test for continuous variables.

We estimated 5-year all-cause mortality, according to GOLD 2015 and 2019 staging systems, using Kaplan-Meier survival statistics. Statistical comparisons were performed using the Log-Rank test Receiver Operation Characteristic (ROC) curve analyses, area under the curve (AUC) and the 95% CI of the AUC were calculated to measure the predictive accuracy for mortality. Also, we compared the prediction ability of mortality on both classifications using sensitivity, positive predictive value and the Youden’s index with Epidat 3.1 program.
Results

We pooled data from 22 COPD cohorts with a total of 17,139 patients, finally including 8,823 patients from 15 cohorts that had all complete variables to be classified as GOLD 2015 and GOLD 2019. A comparison of baseline characteristics of included and not included patients is presented in Table 1. There were statistically significant differences in many variables given the large size, but most should be considered not clinically relevant (Table 1).

The 8,823 included patients were 62.9% male, with a mean age of 63.9 (SD± 9.8) years, mean±SD BMI 27.0±5.8 kg/m\(^2\) and mMRC dyspnoea score of 1.8±1.4. Postbronchodilator FEV\(_1\) was 54.8%±22.3 of the predictive value, and 6-minute walk distance was 376.9±129.1 meters. Based on spirometry staging 1,153 (13%) had mild (stage 1), 3,711 (42.1%) had moderate (stage 2), 2,654 (30.1%) had severe (stage 3) and 1,301 (14.8%) had very severe (stage 4) disease.

The distribution of these 8,823 patients according to GOLD 2015 and GOLD 2019 is presented in Figure 1. With GOLD 2019 there is a shift towards the less severe staging of disease (absolute increase in stage A and B of 7.8% and 22.2% respectively; and absolute decrease in stage C and D of 7.8 and 22.2% respectively).

The overall 5-year mortality rate was 18.3%. The all-cause 5-year mortality rates according to both classifications are shown in Table 2. Figure 2 shows Kaplan-Meier curves for 5-year mortality according to GOLD 2015 (Figure 2A) and GOLD 2019 (Figure 2B). All-cause mortality at 5 years in the 2015 GOLD classification was higher in grade D, followed by grades B, C (with similar mortality), and finally grade A, log-rank test p<0.001 (Table 2 and Figure 2A). Grade D diverged from the beginning of follow up, while grades B and C diverged after 1 year of follow-up. In GOLD 2019, the four Kaplan-Meier curves diverge during the first year, but interestingly, grade B had higher mortality than grade C, so mortality was higher in groups B and D (more symptoms) than in groups A and C (fewer symptoms; Figure 2B). The degree of obstruction measured by FEV\(_1\) % further subclassified patients into 16 subgroups with different mortality rates, increasing from 1A to 4D in GOLD 2019 grading system (Table 3). Figure 3 shows Kaplan-Meier curves for each of the spirometry strata. The higher mortality of group B over group C persisted in each of the strata with the exception of spirometry strata 1, with a higher
mortality in group C. Similarly to GOLD 2015, in GOLD 2019, grade A and D had the lowest and highest mortality, respectively, with very similar absolute numbers (Table 2, Figure 2).

The primary outcome, the prediction capacity as measured by the AUC of ROC curve for mortality up to 5 years was intermediate (<0.70) for both systems (Figure 4). GOLD 2015 exhibited slightly better discrimination in predicting mortality (AUC 0.67 [95% CI 0.66-0.68]) than GOLD 2019 classification (AUC 0.64 [95% CI 0.63-0.66]).

Regarding sensitivity parameters, both classifications had quite shallow values. GOLD 2019 had a higher sensitivity for predicting mortality on A and B groups vs 2015 classification (19.1 vs 11.1 and 43.6 vs 11.6). On the other hand, GOLD 2015 had a higher sensitivity on groups C and D vs 2019 classification (14.6 vs 6.6 and 62.5 vs 30.6) based on overlapping 95% CIs (Table 4). The positive predictive values were also higher in GOLD 2019 group A and B vs the same groups in GOLD 2015 (9.5 vs. 6.9 and 21.2 vs. 13.3); but not different (overlapping confidence intervals) in groups C and D. The Youden indices were quite low for both classifications, even with negative values, showing that it is not an optimal classification system to assess mortality.

Discussion

Our study evaluates mortality according to the last two GOLD classifications, and it is one of the most extensive to date. The most important finding is that the new GOLD 2019 classification (based on symptoms or exacerbations along with stages spirometry analysed altogether) did not predict 5-year mortality better than GOLD 2015 classification (based on spirometry, history of exacerbation and symptoms). How to define and stage COPD exacerbations is a matter of an intense, long debate[15]. Most 3CIA individual cohorts used subsequent iterations of GOLD-accepted definitions in their protocols, mostly based on Rodriguez-Roisin R, et al. seminal paper[16], including mild (symptom-only) exacerbations. However, when pooling for 3CIA, we only focused on those COPD exacerbations that required health services use, ER, admission or death. In GOLD 2019 classification, subgroups B and D had the worse mortality, highlighting that the higher burden of symptoms conveys a higher mortality independently of
spirometry (Table 2 and Figure 2B). Finally, we show an important shift in the proportions of patients between the 2015 and 2019 ABCD grades, with milder severity in GOLD 2019.

GOLD 2015 and GOLD 2019 classifications had a low discriminatory power as per the AUCs, ranging from 0.67 to 0.65, and similar to other studies (by consensus, AUC below 0.70 are considered low or weak)\textsuperscript{[11]}. Sensitivity and positive predictive values indicate that the general performance of the two models is similar and very low. Also, the Youden’s indices are very low with negative values that have no meaningful interpretation in practice. These findings support the results of other studies, suggesting that GOLD classification is not a good predictor for mortality\textsuperscript{[11-12]}. There may be various reasons for these poor results. The main reason is that these classifications were conceived to guide treatment, so it is not surprising that their capacity for predicting mortality is low. There are clinical phenotypes such as the asthma-COPD, the frequent exacerbator with emphysema or chronic bronchitis comorbidities and different indexes, that are significant predictors of mortality and are not entirely included in the GOLD stages\textsuperscript{[17-21]}. In our study, sensitivity and positive predictive value are higher in GOLD 2019 groups A and B. On the contrary, sensitivity is higher in GOLD 2015 in groups C and D. These results suggest that GOLD 2019 predicts slightly better mortality on low risk groups (A and B) and GOLD 2015 in high risk groups (C and D), requiring more studies to corroborate it.

The discriminatory power of GOLD 2019 was lower than GOLD 2015 as shown in AUCs values. The partition of FEV\textsubscript{1} as a direct classifier in GOLD 2019 reduced ability to discriminate survival, highlighting the need to consider the severity of airflow obstruction in assessing mortality risk. When using GOLD 2019 with a composite of spirometry, exacerbations and symptoms (16 subgroups 1A to 4D classification), we found an increase in all-cause mortality between GOLD 2019 stage 1 and GOLD 2019 stage 4 across grades A, B and D, highlighting the persisting importance of FEV\textsubscript{1} as a predictor of mortality (Table 3 and Figure 3). In group C, mortality was higher in spirometry stage 1 than in 2, probably due to a significant difference of the proportion in patients between the two stages.
Our study confirms that patients classified as GOLD A had the best survival, and patients with GOLD D, the higher mortality in both classifications\cite{22-24}. Mortality of groups B and C in GOLD 2015 lied in between A and D groups and often overlapped. In GOLD 2019 mortality was significantly higher in group B patients than in group C. This finding is similar as other previous reports published\cite{25-27}, showing that group B is an intermediate-high risk group associated with more exacerbations and likely to other comorbidities that may cause dyspnoea (such as heart failure). Furthermore, we show that the burden of symptoms (represented by groups B and D) have a prognostic value additive but independent to spirometry.

The current study demonstrates that the use of GOLD 2019 classification scheme shifted patients with COPD to groups of milder severity compared with GOLD 2015. This happened in keeping with previous reports, but in a smaller proportion of patients (30% of patients reassigned towards group A or B compared to 53% in Lee et al study or 66% in Tan et al study)\cite{28-29}. The further distribution of spirometric parameters from two categories in GOLD 2015 (FEV\textsubscript{1} less or higher than 50%) to four categories in GOLD 2019, was one of the possible reasons for the patient’s shift from C and D in GOLD 2015 to A and B groups in GOLD 2019. This phenomenon is opposed to the one observed with the use of the revised GOLD 2011 classification, which shifted the patients from the GOLD 2007 towards more advanced stages of the disease (D group increased almost 3 times)\cite{7}. Remarkably, in both classifications, group C was consistently the smallest group (Figure 1), as seen in other reports\cite{27}. The implication of progressively milder disease classifications for the treatment choices clinicians make in real life practice guided by GOLD is not yet clear given the recent nature of the latest GOLD iteration, but will be important to monitor.

Strength of our study include a large sample size, the study design (a pooled-analysis of individual patient-data from several cohorts), and the different degrees of severity of patients from different cohorts, maximizing its high external validity. Prospective data collection of spirometry with a post-bronchodilator test, dyspnea by mMRC scale, history of exacerbation and mortality
enabled direct classification of patients by 2015 and 2019 GOLD staging schemes. We also have a significant representation of women, of which other COPD studies might not have achieved\[30\].

Our study has several limitations. First, although we started with 17,139 patients with COPD, a considerable number of patients were excluded because of missing information on key variables, mainly regarding the history of exacerbations. These missing data are unlikely to affect the validity of our results, as we can see in our analysis comparing included and non-included patients. Second, the mortality analysis used all-cause death, and we have no data regarding specific causes of death (this data was not collected consistently in all cohorts). Third, symptoms were only evaluated using mMRC dyspnea score, but not with the COPD Assessment Test, or other instruments\[31\]; however, that is in line with other reported cohorts\[32-33\]. Fourth, most patients came from hospital-based cohorts, so we likely have more patients with moderate to severe disease and less patients with mild and moderate disease compared to an outpatient setting, or a primary care population. Indeed, the 22 cohorts from eleven countries in 3CIA within our initiative are only a sample representing the estimated 300 million COPD patients worldwide\[34\]. Finally, the recruitment timeframe was long (10 years), so evolving treatment recommendations might influence results.

In conclusion, this study of COPD cohorts, including 8823 patients, showed that neither GOLD 2015 nor GOLD 2019 are strong predictors of mortality. GOLD 2019 predicted mortality better than GOLD 2015 in groups A and B but worse in groups C and D. However, none of the GOLD classifications has sufficient discriminatory power to be used as a tool for risk classification of mortality in patients with COPD. Ours should be considered a constructive exercise and a critical appraisal of the last two GOLD iterations defining COPD. Within 3CIA, we have already suggested several proposals for future COPD staging and grading classifications, by applying more evidence-based thresholds of evidence-based variables [35-39].
Declaration of interest

There are no direct or indirect conflicts of interest to disclose related with this manuscript.

References


https://mc.manuscriptcentral.com/erjor


[27] Flynn RWV, MacDonald TM, Chalmers JD, Schembri S. The effect of changes to GOLD severity stage on long term morbidity and mortality in COPD. Respir Res. 2018;19:249.


https://mc.manuscriptcentral.com/erjor


<table>
<thead>
<tr>
<th></th>
<th>Excluded (n=8316)</th>
<th>Included (n=8823)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.2 ± 10.7</td>
<td>63.9 ± 9.8</td>
<td>0.08</td>
</tr>
<tr>
<td>Male sex</td>
<td>6232 (74.9%)</td>
<td>5552 (62.9%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>26.5 ± 4.9</td>
<td>27.0 ± 5.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Modified MRC dyspnea scale 0</td>
<td>1647 (23.4%)</td>
<td>1957 (22.2%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Modified MRC dyspnea scale 1</td>
<td>2261 (32.1%)</td>
<td>1886 (21.4%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Modified MRC dyspnea scale 2</td>
<td>1641 (23.3%)</td>
<td>1772 (20.1%)</td>
<td></td>
</tr>
<tr>
<td>Modified MRC dyspnea scale 3</td>
<td>688 (9.8%)</td>
<td>1951 (22.1%)</td>
<td></td>
</tr>
<tr>
<td>Modified MRC dyspnea scale 4</td>
<td>805 (11.4%)</td>
<td>1257 (14.3%)</td>
<td></td>
</tr>
<tr>
<td>Six-minute walk distance (meters)</td>
<td>415.4 ± 108.8</td>
<td>376.9 ± 129.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FEV₁ post BD (ml)</td>
<td>1.7 ± 0.7</td>
<td>1.6 ± 0.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FEV₁ post BD (%)</td>
<td>60.8 ± 22.1</td>
<td>54.8 ± 22.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Former</td>
<td>3989 (49.1%)</td>
<td>5392 (61.4%)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>3589 (44.2%)</td>
<td>3174 (36.1%)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>542 (6.7%)</td>
<td>222 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>Pack-years</td>
<td>46.4 ± 28.8</td>
<td>42.1 ± 28.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cough</td>
<td>1103 (54.2%)</td>
<td>342 (43.9%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sputum</td>
<td>1159 (42.1%)</td>
<td>341 (43.9%)</td>
<td>0.353</td>
</tr>
<tr>
<td>Diabetes</td>
<td>354 (6.7%)</td>
<td>303 (16.6%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>1072 (30.8%)</td>
<td>467 (25.9%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>166 (38.7%)</td>
<td>787 (69.5%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>454 (40.4%)</td>
<td>826 (44.8%)</td>
<td>0.028</td>
</tr>
</tbody>
</table>
### Table 1:
Comparison of demographic and clinical characteristics in 3CIA COPD patients included/excluded in this analysis

<table>
<thead>
<tr>
<th></th>
<th>Included</th>
<th>Excluded</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>1243 (26.1%)</td>
<td>209 (10.7%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Spirometry staging</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1</td>
<td>1567(19%)</td>
<td>1153(13.1%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3892(47.1%)</td>
<td>3711(42.1%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2126(25.8%)</td>
<td>2654(30.1%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>671(8.1%)</td>
<td>1301(14.8%)</td>
<td></td>
</tr>
<tr>
<td>Long term oxygen therapy</td>
<td>119 (1.4%)</td>
<td>430 (4.8%)</td>
<td>0.259</td>
</tr>
</tbody>
</table>

Data are n (%), mean (SD) or median (IQR). BMI: Body mass index (kg/m²). MRC: Medical Research Council. FEV₁: forced expiratory volume in 1 second. BD: bronchodilator.
Table 2: Mortality risk among COPD patients according to GOLD 2019 and GOLD 2015 classifications

<table>
<thead>
<tr>
<th>Group</th>
<th>GOLD 2015 5-year mortality</th>
<th>GOLD 2019 5-year mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>5.8 %</td>
<td>7.5 %</td>
</tr>
<tr>
<td>Group B</td>
<td>13.8 %</td>
<td>23.2 %</td>
</tr>
<tr>
<td>Group C</td>
<td>14.1 %</td>
<td>14.8 %</td>
</tr>
<tr>
<td>Group D</td>
<td>30.8 %</td>
<td>32.8 %</td>
</tr>
</tbody>
</table>
Table 3: Five-year all-cause mortality among spirometry strata within GOLD 2019 ABCD classification

<table>
<thead>
<tr>
<th>GOLD 2019</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spirometry I</td>
<td>3.4%</td>
<td>9.8%</td>
<td>16.2%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Spirometry II</td>
<td>7%</td>
<td>14.9%</td>
<td>8.3%</td>
<td>22.1%</td>
</tr>
<tr>
<td>Spirometry III</td>
<td>13%</td>
<td>23.7%</td>
<td>17.7%</td>
<td>32.6%</td>
</tr>
<tr>
<td>Spirometry IV</td>
<td>16.7%</td>
<td>39.1%</td>
<td>29.5%</td>
<td>46%</td>
</tr>
</tbody>
</table>
Table 4: Accuracy for predicting mortality of the ABCD groups classifications by GOLD 2015 and GOLD 2019 schemes

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>Sensitivity (% 95 CI)</th>
<th>PPV (% 95 CI)</th>
<th>Indice de Youden (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 2015 group A</td>
<td>11.1 (9.6-12.7)</td>
<td>6.9 (5.9-7.9)</td>
<td>-0.23 (-0.25 – -0.22)</td>
</tr>
<tr>
<td>GOLD 2015 group B</td>
<td>11.6 (10-13.2)</td>
<td>13.3 (11.5-15.1)</td>
<td>-0.06 (-0.08 – -0.04)</td>
</tr>
<tr>
<td>GOLD 2015 group C</td>
<td>14.6 (12.8-16.4)</td>
<td>20.2 (17.9-22.6)</td>
<td>+0.01 (-0.01 – +0.03)</td>
</tr>
<tr>
<td>GOLD 2015 group D</td>
<td>62.5 (60.1-64.9)</td>
<td>29.5 (28-31.1)</td>
<td>+0.28 (+0.25 – +0.31)</td>
</tr>
<tr>
<td>GOLD 2019 group A</td>
<td>19.1 (17.2-21.1)</td>
<td>9.5 (8.4-10.5)</td>
<td>-0.23 (-0.25 – -0.21)</td>
</tr>
<tr>
<td>GOLD 2019 group B</td>
<td>43.6 (41.1-46.1)</td>
<td>21.2 (19.8-22.6)</td>
<td>+0.06 (+0.03 – +0.09)</td>
</tr>
<tr>
<td>GOLD 2019 group C</td>
<td>6.6 (5.3-7.8)</td>
<td>21.7 (18-25.5)</td>
<td>+0.01 (0.0 – +0.02)</td>
</tr>
<tr>
<td>GOLD 2019 group D</td>
<td>30.6 (28.3-32.8)</td>
<td>32.8 (30.4-35.2)</td>
<td>+0.16 (+0.14 – +0.18)</td>
</tr>
</tbody>
</table>

PPV: Positive predictive value. CI: confidence interval
TABLES AND FIGURES:

Table 1: Comparison of demographic and clinical characteristics in 3CIA COPD patients included/excluded in this analysis

Table 2: Mortality risk among COPD patients according to GOLD 2019 and GOLD 2015 classifications

Table 3: Five-year all-cause mortality among spirometry strata within GOLD 2019 ABCD classification

Table 4: Accuracy for predicting mortality of the ABCD groups classifications by GOLD 2015 and GOLD 2019 schemes

Figure 1: Distribution of participants by classification in GOLD 2015 and GOLD 2019

Figure 2: Kaplan-Meier survival curves by GOLD 2015 and GOLD 2019

Figure 3: Kaplan-Meier survival curves by GOLD 2019 and spirometry subgroups (IA-IVD)

Figure 4: Receiver operating curves for all cause mortality at 5 years follow-up
Mortality prediction in chronic obstructive pulmonary disease comparing the GOLD 2015 and GOLD 2019 staging: a pooled analysis of individual patient data

Elena García Castillo1 *, Tamara Alonso Pérez1 *, Julio Ancochea1, Maria Teresa Pastor Sanz1, Pere Almagro2, Pablo Martínez-Camblor3, Marc Miravitlles4, Mónica Rodríguez-Carballeira5, Annie Navarro6, Bernd Lamprecht7, Ana S Ramirez-García Luna8, Bernhard Kaiser9, Inmaculada Alfageme10, Ciro Casanova11, Cristóbal Esteban12, Juan J Soler-Cataluña13, Juan P de-Torres14, Bartolomé R Celli15, Jose M Marín16, Gerben ter Riet17, Patricia Sobradillo18, Peter Lange19, Judith García-Aymerich20,21,22, Josep M Anto20,21,22, Alice M Turner23, MeiLan K Han24, Arnulf Langhammer25, Sigrid Anna Aalberg Vikjord25, Alice Sternberg26, Linda Leivseth27, Per Bakke28, Ane Johannessen29, Toru Oga30, Borja Cosío31, Andrés Echazarreta32, Nicolás Roche33, Pierre-Régis Burgel34, Don D Sin, Milo34,35, Milo A Puhan36, Jose Luis López Campos37, Laura Carrasco38, Joan B Soriano39 & for the 3CIA collaboration.

* Shared first authors

Author information:

1. Pneumology Department, Hospital Universitario de la Princesa. Instituto de Investigación Hospital Universitario de la Princesa (IISP), Universidad Autónoma de Madrid, Madrid, Spain.
2. Multimorbidity Patients Unit, Internal Medicine Dept, University Hospital Mutua de Terrassa, University of Barcelona, Barcelona, Spain.
3. Geisel School of Medicine at Dartmouth, Hanover, NH, USA.
4. Pneumology Department, Hospital Universitary Vall d’Hebron, CIBER de Enfermedades Respiratorias (CIBERES), Barcelona, Spain.
5. Multimorbidity Patients Unit, Internal Medicine, Hospital Universitari Mutua de Terrassa, Universitat de Barcelona, Barcelona, Spain.
6. Pneumology Service, Hospital Universitari Mútua Terrassa, Barcelona, Spain.
7. Department of Pulmonary Medicine, Kepler-University-Hospital. Faculty of Medicine, Johannes-Kepler-University Linz, Austria.
8. Facultad de Medicina, Universidad Autónoma de San Luis Potosí, San Luis Potosí, Mexico.
9. Department of Pulmonary Medicine, Paracelsus Medical University Hospital, Salzburg, Austria.
11. Hospital Universitario Nuestra Señora de La Candelaria, Universidad de La Laguna, Tenerife, Spain.
15. Pulmonary and Critical Care Medicine, Harvard University, Brigham and Women's Hospital, Boston, MA, USA.
16. Hospital Universitario Miguel Servet, Zaragoza, and CIBER de Enfermedades Respiratorias (CIBERES), Spain.
17. Department of General Practice, Academic Medical Center, University of Amsterdam (AMC), Amsterdam, The Netherlands.
18. Hospital Universitario Araba, Sede Txagorritxu, Vitoria, Spain for University Hospital of Cruces in Barakaldo, Spain.
19. Section of Social Medicine, Department of Public Health, Copenhagen University, Copenhagen City Heart Study, Frederiksberg Hospital, Frederiksberg, Copenhagen, Denmark.
20. Global, Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain.
21. Department of Experimental and Health Sciences, Universitat Pompeu Fabra (UPF), Barcelona, Spain.
22. CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain.
23. Institute of Applied Health Research, University of Birmingham, Edgbaston, UK.
24. Internal Medicine, Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, MI, USA.
25. Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Trondheim, Norway.
26. Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA.
27. Centre for Clinical Documentation and Evaluation, Northern Norway Regional Health Authority, Tromso, Norway.
29. Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway.
30. Department of Respiratory Care and Sleep Control Medicine, Kyoto University, Kyoto, Japan.
31. Department of Respiratory Medicine, Hospital Son Espases-IdISPa, Ciberes, Mallorca, Spain.
32. Servicio de Neumonología, Hospital San Juan de Dios de La Plata, Buenos Aires, Argentina.
33. Respiratory Medicine, Cochin Hospital APHP, University Paris Descartes, Paris, France.
34. James Hogg Research Centre, University of British Columbia, Vancouver, BC, Canada.
35. Division of Respiratory Medicine, Department of Medicine, St Paul's Hospital, Vancouver, BC, Canada.
36. Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland.
37. Pulmonology Department. Hospital Universitario Virgen del Rocio, Sevilla, España.
38. Pulmonology Department. Hospital Universitario Virgen del Rocio, Sevilla, España.
39. Instituto de Investigación Hospital Universitario de la Princesa (IISP), Universidad Autónoma de Madrid, Madrid, Spain

Address for correspondence:

Dr. Joan B Soriano
Hospital Universitario de la Princesa, Diego de León 62, Neumología 6ª planta, 28006-Madrid, Spain
Email: jbsoriano2@gmail.com
Cellular: +34 618 86 77 69

File information:
Date: July/April, 2020
Word count: 23,838 words
References: 394 references
Illustrations: 4 tables and 4 figures
Keywords: COPD, mortality, survival
Mortality prediction in chronic obstructive pulmonary disease comparing the GOLD 2015 and GOLD 2019 staging: a pooled analysis of individual patient data

Abstract

In 2019, The Global Initiative for Chronic Obstructive Lung Disease (GOLD) modified the grading system for patients with chronic obstructive pulmonary disease (COPD) creating 16 subgroups (1A-4D). As part of the COPD Cohorts Collaborative International Assessment (3CIA) initiative, we aim to compare mortality prediction of 2015 and 2019 COPD GOLD staging systems.

We studied 17 139 COPD patients from the 3CIA study, selecting those with complete data. Patients were classified by the 2015 and 2019 GOLD ABCD systems and we compared the predictive ability for 5-year mortality of both classifications.

17 139 patients with COPD were enrolled in 22 cohorts of 11 countries between 2003 to 2017; 8 823 of them had complete data and were analyzed. Mean age was 63.9 years (SD 9.8) and 62.9% were male. GOLD 2019 classified the patients in milder degrees of COPD. For both classifications, group D had higher mortality. Five-year mortality did not differ between groups B and C in GOLD 2015; in GOLD 2019, mortality was greater for group B than C. Patients classified as group A and B had better sensitivity and positive predictive value with GOLD 2019 classification than GOLD 2015. GOLD 2015 had better sensitivity for group C and D than GOLD 2019. The AUC for 5-year mortality were only 0.67 (95% CI 0.66-0.68) for GOLD 2015 and 0.65 (95% CI 0.63-0.66) for GOLD 2019.

The new GOLD 2019 classification does not predict mortality better than the previous GOLD 2015 system.

Take Home message:

GOLD 2019 staging system created 16 subgroups
GOLD 2015 and GOLD 2019 are not strong predictors of mortality and don’t have sufficient discriminatory power to be used as a tool for risk classification of mortality in patients with COPD.
Introduction

Chronic obstructive pulmonary disease (COPD) is a common cause of morbidity and mortality in the world. COPD affects approximately 328 million people worldwide, and COPD related deaths amount to 4 million deaths every year\(^1\). Assessment of disease severity is essential to predict prognosis and to standardize treatment regimes. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) document is the most widely used treatment guide for the staging and management of COPD. The GOLD grading system for COPD has significantly evolved since first publication in 2001 to the current version in 2019. Initially, in the GOLD 2007 classification, only post-bronchodilator airflow limitation based on spirometry forced expiratory volume in 1 second (FEV\(_1\)) was used to grade the severity of COPD\(^2\). Later on, some criticism arose on this grading score because it relied only upon FEV\(_1\) which is not a good predictor of dyspnoea, quality of life or exercise tolerance. Further, other important variables to evaluate prognosis in COPD, such as sub-phenotypes, exacerbations, dyspnoea severity or comorbidities have been proposed, among others. Therefore, GOLD 2011 proposed a classification system of four groups, ABCD, combining FEV\(_1\) and two clinical parameters: history of exacerbations and respiratory symptoms measured by the modified Medical Research Council (mMRC) dyspnoea score, or the COPD Assesment Test score (CAT)\(^3\). The 2011 ABCD classification was considered an improvement in the management of patients with COPD, providing an opportunity to further guide the individualized care of these patients. GOLD 2011 predicted future exacerbations better than GOLD 2007 but there was no difference in mortality predictions or respiratory outcomes\(^4-7\). In 2015 an updated report was published with the same measurement parameters (FEV\(_1\), dyspnoea and exacerbations) than 2011 classification\(^8\).

The latest GOLD update, published in 2019 uses a composite of spirometry, symptoms and exacerbations, but importantly separating the spirometric 1-4 staging from the ABCD groups\(^9\). This separation is relevant because it is known there are differences in the rate of exacerbations for the most severe COPD patients, depending on whether the risk is based on pulmonary function tests, on the history of exacerbations or both\(^10\). All these classifications were
initially designed not to assess prognosis, but to aid clinicians in creating optimal treatment
regimes for patients. Thus, the prognostic ability of GOLD 2019 compared to previous
classifications is largely unknown, with only a few published studies\cite{11,12}. To address this issue,
we used pooled data from 17,139 patients of 22 COPD cohorts and eleven countries and compared
the prognostic capacity of the 2019 versus 2015 GOLD staging classifications to predict mortality.

Methods

Study population

In this international study, we assessed 17,139 patients from the COPD Cohorts
Collaborative International Assessment (3CIA) initiative. All were prospective cohorts that
recruited patients within the period 1999 to 2017, except one of them that was a population based
cohort. All patients had a definition of COPD characterized by spirometry, that is post-
bronchodilator FEV\textsubscript{1} to forced vital capacity ratio (FVC) ratio less than 0.7 and a clinical
diagnosis of COPD. Spirometry was performed using the standards provided by the American
Thoracic Society and European Respiratory Society\cite{13}. The primary investigators of each of the
participating 3CIA cohorts provided individual patient's data for pooled analysis. We obtained a
minimum individual dataset including the vital status (up to death, right truncation or 2017), age,
sex, smoking status, pre-bronchodilator and post-bronchodilator FEV\textsubscript{1} and FVC and dyspnoea
measured with the modified mMRC, among others\cite{14}. Only in a number of 3CIA cohorts were
data of number of exacerbations in the previous year available. For the current study, we selected
exclusively those cohorts in which the number of exacerbations in the previous year were
available in the database, since this variable is required to calculate the GOLD 2015 and 2019
grading systems. Fifteen out of a total of 22 cohorts contained data on history of exacerbations,
so that the final number of patients available to be classified according to GOLD 2015 and GOLD
2019 was 8,823. Symptoms were assessed using the mMRC dyspnoea scale. To determine the
risk descriptor in the 2015 grouping system, we used exacerbations history and GOLD spirometry
stages. The combination of symptoms (mMRC) and the worse risk descriptor (spirometry or
exacerbation history) were used to classify patients by GOLD 2015 system. Participants were classified using the GOLD 2019 system into four grades (1-4) based on postbronchodilator FEV\textsubscript{1} percentage of prediction as stage 1 (FEV\textsubscript{1} ≥ 80), stage 2 (FEV\textsubscript{1} 79-50), stage 3 (FEV\textsubscript{1} 30-49) and stage 4 (FEV\textsubscript{1} < 30). Groups ABCD were defined by self-reported severity of dyspnea (mMRC) and number of exacerbations in the previous year.

All participants provided informed written consent, and each study was conducted with the formal approval of the local ethics institutional committees following the principles of the Declaration of Helsinki.

Outcomes

The primary outcome was the prediction ability of all-cause mortality in the individuals by the two GOLD systems.

Statistical analysis

The 3CIA database manager quality-controlled all data centrally and created a clean database with a data dictionary. All implausible or missing variables were queried with the original study investigators, and datum were removed from the central database if errors could not be corrected. Because the cohorts had different follow-up times, patients were right-censored at five years of follow-up.

Descriptive statistics used mean and standard deviation for continuous variables and the number of cases and percentages for categorical variables. Comparisons between groups were performed with the Chi\textsuperscript{2} test for categorical variables and the T-test for continuous variables.

We estimated 5-year all-cause mortality, according to GOLD 2015 and 2019 staging systems, using Kaplan-Meier survival statistics. Statistical comparisons were performed using the Log-Rank test Receiver Operation Characteristic (ROC) curve analyses, area under the curve (AUC) and the 95% CI of the AUC were calculated to measure the predictive accuracy for mortality. Also, we compared the prediction ability of mortality on both classifications using sensitivity, positive predictive value and the Youden’s index with Epidat 3.1 program.
Results

We pooled data from 22 COPD cohorts with a total of 17,139 patients, finally including 8,823 patients from 15 cohorts that had all complete variables to be classified as GOLD 2015 and GOLD 2019. A comparison of baseline characteristics of included and not included patients is presented in Table 1. There were statistically significant differences in many variables given the large size, but most should be considered not clinically relevant (Table 1).

The 8,823 included patients were 62.9% male, with a mean age of 63.9 (SD± 9.8) years, mean±SD BMI 27.0±5.8 kg/m² and mMRC dyspnoea score of 1.8±1.4. Postbronchodilator FEV₁ was 54.8%±22.3 of the predictive value, and 6-minute walk distance was 376.9±129.1 meters. Based on spirometry staging 1,153 (13%) had mild (stage 1), 3,711 (42.1%) had moderate (stage 2), 2,654 (30.1%) had severe (stage 3) and 1,301 (14.8%) had very severe (stage 4) disease.

The distribution of these 8,823 patients according to GOLD 2015 and GOLD 2019 is presented in Figure 1. With GOLD 2019 there is a shift towards the less severe staging of disease (absolute increase in stage A and B of 7.8% and 22.2% respectively; and absolute decrease in stage C and D of 7.8 and 22.2% respectively).

The overall 5-year mortality rate was 18.3%. The all-cause 5-year mortality rates according to both classifications are shown in Table 2. Figure 2 shows Kaplan-Meier curves for 5-year mortality according to GOLD 2015 (Figure 2A) and GOLD 2019 (Figure 2B). All-cause mortality at 5 years in the 2015 GOLD classification was higher in grade D, followed by grades B, C (with similar mortality), and finally grade A, log-rank test p<0.001 (Table 2 and Figure 2A). Grade D diverged from the beginning of follow up, while grades B and C diverged after 1 year of follow-up. In GOLD 2019, the four Kaplan-Meier curves diverge during the first year, but interestingly, grade B had higher mortality than grade C, so mortality was higher in groups B and D (more symptoms) than in groups A and C (fewer symptoms; Figure 2B). The degree of obstruction measured by FEV₁ % further subclassified patients into 16 subgroups with different mortality rates, increasing from 1A to 4D in GOLD 2019 grading system (Table 3). Figure 3 shows Kaplan-Meier curves for each of the spirometry strata. The higher mortality of group B
over group C persisted in each of the strata with the exception of spirometry strata 1, with a higher mortality in group C. Similarly to GOLD 2015, in GOLD 2019, grade A and D had the lowest and highest mortality, respectively, with very similar absolute numbers (Table 2, Figure 2).

The primary outcome, the prediction capacity as measured by the AUC of ROC curve for mortality up to 5 years was intermediate (<0.70) for both systems (Figure 4). GOLD 2015 exhibited slightly better discrimination in predicting mortality (AUC 0.67 [95% CI 0.66-0.68]) than GOLD 2019 classification (AUC 0.64 [95% CI 0.63-0.66]).

Regarding sensitivity parameters, both classifications had quite shallow values. GOLD 2019 had a higher sensitivity for predicting mortality on A and B groups vs 2015 classification (19.1 vs 11.1 and 43.6 vs 11.6). On the other hand, GOLD 2015 had a higher sensitivity on groups C and D vs 2019 classification (14.6 vs 6.6 and 62.5 vs 30.6) based on overlapping 95% CIs (Table 4). The positive predictive values were also higher in GOLD 2019 group A and B vs the same groups in GOLD 2015 (9.5 vs. 6.9 and 21.2 vs. 13.3); but not different (overlapping confidence intervals) in groups C and D. The Youden indices were quite low for both classifications, even with negative values, showing that it is not an optimal classification system to assess mortality.

Discussion

Our study evaluates mortality according to the last two GOLD classifications, and it is one of the most extensive to date. The most important finding is that the new GOLD 2019 classification (based on symptoms or exacerbations along with stages spirometry analysed altogether) did not predict 5-year mortality better than GOLD 2015 classification (based on spirometry, history of exacerbation and symptoms). How to define and stage COPD exacerbations is a matter of an intense, long debate\textsuperscript{[15]}. Most 3CIA individual cohorts used subsequent iterations of GOLD-accepted definitions in their protocols, mostly based on Rodriguez-Roisin R, et al. seminal paper\textsuperscript{[16]}, including mild (symptom-only) exacerbations. However, when pooling for 3CIA, we only focused on those COPD exacerbations that required health services use, ER, admission or death. In GOLD 2019 classification, subgroups B and D had the worse mortality,
highlighting that the higher burden of symptoms conveys a higher mortality independently of spirometry (Table 2 and Figure 2B). Finally, we show an important shift in the proportions of patients between the 2015 and 2019 ABCD grades, with milder severity in GOLD 2019.

GOLD 2015 and GOLD 2019 classifications had a low discriminatory power as per the AUCs, ranging from 0.67 to 0.65, and similar to other studies (by consensus, AUC below 0.70 are considered low or weak). Sensitivity and positive predictive values indicate that the general performance of the two models is similar and very low. Also, the Youden’s indices are very low with negative values that have no meaningful interpretation in practice. These findings support the results of other studies, suggesting that GOLD classification is not a good predictor for mortality. There may be various reasons for these poor results. The main reason is that these classifications were conceived to guide treatment, so it is not surprising that their capacity for predicting mortality is low. There are clinical phenotypes such as the asthma-COPD, the frequent exacerbator with emphysema or chronic bronchitis comorbidities and different indexes, that are significant predictors of mortality and are not entirely included in the GOLD stages. In our study, sensitivity and positive predictive value are higher in GOLD 2019 groups A and B. On the contrary, sensitivity is higher in GOLD 2015 in groups C and D. These results suggest that GOLD 2019 predicts slightly better mortality on low risk groups (A and B) and GOLD 2015 in high risk groups (C and D), requiring more studies to corroborate it.

The discriminatory power of GOLD 2019 was lower than GOLD 2015 as shown in AUCs values. The partition of FEV$_1$ as a direct classifier in GOLD 2019 reduced ability to discriminate survival, highlighting the need to consider the severity of airflow obstruction in assessing mortality risk. When using GOLD 2019 with a composite of spirometry, exacerbations and symptoms (16 subgroups 1A to 4D classification), we found an increase in all-cause mortality between GOLD 2019 stage 1 and GOLD 2019 stage 4 across grades A, B and D, highlighting the persisting importance of FEV$_1$ as a predictor of mortality (Table 3 and Figure 3). In group C, mortality was higher in spirometry stage 1 than in 2, probably due to a significant difference of the proportion in patients between the two stages.
Our study confirms that patients classified as GOLD A had the best survival, and patients with GOLD D, the higher mortality in both classifications\[^220-242\]. Mortality of groups B and C in GOLD 2015 lied in between A and D groups and often overlapped. In GOLD 2019 mortality was significantly higher in group B patients than in group C. This finding is similar as other previous reports published\[^253-275\], showing that group B is an intermediate-high risk group associated with more exacerbations and likely to other comorbidities that may cause dyspnoea (such as heart failure). Furthermore, we show that the burden of symptoms (represented by groups B and D) have a prognostic value additive but independent to spirometry.

The current study demonstrates that the use of GOLD 2019 classification scheme shifted patients with COPD to groups of milder severity compared with GOLD 2015. This happened in keeping with previous reports, but in a smaller proportion of patients (30% of patients reassigned towards group A or B compared to 53% in Lee et al study or 66% in Tan et al study)\[^286-297\]. The further distribution of spirometric parameters from two categories in GOLD 2015 (FEV\(_1\) less or higher than 50%) to four categories in GOLD 2019, was one of the possible reasons for the patient’s shift from C and D in GOLD 2015 to A and B groups in GOLD 2019. This phenomenon is opposed to the one observed with the use of the revised GOLD 2011 classification, which shifted the patients from the GOLD 2007 towards more advanced stages of the disease (D group increased almost 3 times)\[^7\]. Remarkably, in both classifications, group C was consistently the smallest group (Figure 1), as seen in other reports\[^224\]. The implication of progressively milder disease classifications for the treatment choices clinicians make in real life practice guided by GOLD is not yet clear given the recent nature of the latest GOLD iteration, but will be important to monitor.

Strength of our study include a large sample size, the study design (a pooled-analysis of individual patient-data from several cohorts), and the different degrees of severity of patients from different cohorts, maximizing its high external validity. Prospective data collection of spirometry with a post-bronchodilator test, dyspnea by mMRC scale, history of exacerbation and mortality enabled direct classification of patients by 2015 and 2019 GOLD staging schemes. We also have
a significant representation of women, of which other COPD studies might not have achieved.\textsuperscript{30}

Our study has several limitations. First, although we started with 17,139 patients with COPD, a considerable number of patients were excluded because of missing information on key variables, mainly regarding the history of exacerbations. These missing data are unlikely to affect the validity of our results, as we can see in our analysis comparing included and non-included patients. Second, the mortality analysis used all-cause death, and we have no data regarding specific causes of death (this data was not collected consistently in all cohorts). Third, symptoms were only evaluated using mMRC dyspnea score, but not with the COPD Assessment Test, or other instruments;\textsuperscript{31} however, that is in line with other reported cohorts.\textsuperscript{32} Fourth, most patients came from hospital-based cohorts, so we likely have more patients with moderate to severe disease and less patients with mild and moderate disease compared to an outpatient setting, or a primary care population. Indeed, the 22 cohorts from eleven countries in 3CIA within our initiative are only a sample representing the estimated 300 million COPD patients worldwide.\textsuperscript{34} Finally, the recruitment timeframe was long (10 years), so evolving treatment recommendations might influence results.

In conclusion, this study of COPD cohorts, including 8823 patients, showed that neither GOLD 2015 nor GOLD 2019 are strong predictors of mortality. GOLD 2019 predicted mortality better than GOLD 2015 in groups A and B but worse in groups C and D. However, none of the GOLD classifications has sufficient discriminatory power to be used as a tool for risk classification of mortality in patients with COPD. Ours should be considered a constructive exercise and a critical appraisal of the last two GOLD iterations defining COPD. Within 3CIA, we have already suggested several proposals for future COPD staging and grading classifications, by applying more evidence-based thresholds of evidence-based variables.\textsuperscript{35-39}
Declaration of interest

There are no direct or indirect conflicts of interest to disclose related with this manuscript

References


Flynn RWV, MacDonald TM, Chalmers JD, Schembri S. The effect of changes to GOLD severity stage on long term morbidity and mortality in COPD. Respir Res. 2018;19:249.


<table>
<thead>
<tr>
<th></th>
<th>Excluded (n=8316)</th>
<th>Included (n=8823)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.2 ± 10.7</td>
<td>63.9 ± 9.8</td>
<td>0.08</td>
</tr>
<tr>
<td>Male sex</td>
<td>6232 (74.9%)</td>
<td>5552 (62.9%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>26.5 ± 4.9</td>
<td>27.0 ± 5.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Modified MRC dyspnea scale</td>
<td>1.5 ± 1.3</td>
<td>1.8 ± 1.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>0</td>
<td>1647 (23.4%)</td>
<td>1957(22.2%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2261(32.1%)</td>
<td>1886(21.4%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2</td>
<td>1641(23.3%)</td>
<td>1772(20.1%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>688(9.8%)</td>
<td>1951(22.1%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>805(11.4%)</td>
<td>1257(14.3%)</td>
<td></td>
</tr>
<tr>
<td>Six-minute walk distance (meters)</td>
<td>415.4 ± 108.8</td>
<td>376.9 ± 129.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FEV₁ post BD (ml)</td>
<td>1.7 ± 0.7</td>
<td>1.6 ± 0.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FEV₁ post BD (%)</td>
<td>60.8 ± 22.1</td>
<td>54.8 ± 22.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Former</td>
<td>3989 (49.1%)</td>
<td>5392 (61.4%)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>3589 (44.2%)</td>
<td>3174 (36.1%)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>542 (6.7%)</td>
<td>222 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>Pack-years</td>
<td>46.4 ± 28.8</td>
<td>42.1 ± 28.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cough</td>
<td>1103 (54.2%)</td>
<td>342 (43.9%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sputum</td>
<td>1159 (42.1%)</td>
<td>341 (43.9%)</td>
<td>0.353</td>
</tr>
<tr>
<td>Diabetes</td>
<td>354 (6.7%)</td>
<td>303 (16.6%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>1072 (30.8%)</td>
<td>467 (25.9%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>166 (38.7%)</td>
<td>787 (69.5%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>454 (40.4%)</td>
<td>826 (44.8%)</td>
<td>0.028</td>
</tr>
</tbody>
</table>
### Table 1:

Comparison of demographic and clinical characteristics in 3CIA COPD patients included/excluded in this analysis

<table>
<thead>
<tr>
<th>Asthma</th>
<th>1243 (26.1%)</th>
<th>209 (10.7%)</th>
<th>&lt; 0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spirometry staging</td>
<td>1</td>
<td>1567(19%)</td>
<td>1153(13.1%)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3892(47.1%)</td>
<td>3711(42.1%)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2126(25.8%)</td>
<td>2654(30.1%)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>671(8.1%)</td>
<td>1301(14.8%)</td>
</tr>
<tr>
<td>Long term oxygen therapy</td>
<td>1</td>
<td>119 (1.4%)</td>
<td>430 (4.8%)</td>
</tr>
</tbody>
</table>

Data are n (%), mean (SD) or median (IQR). BMI: Body mass index (kg/m$^2$). MRC: Medical Research Council. FEV$_1$: forced expiratory volume in 1 second. BD: bronchodilator.
Table 2: Mortality risk among COPD patients according to GOLD 2019 and GOLD 2015 classifications

<table>
<thead>
<tr>
<th></th>
<th>GOLD 2015 5-year mortality</th>
<th>GOLD 2019 5-year mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>5.8 %</td>
<td>7.5 %</td>
</tr>
<tr>
<td>Group B</td>
<td>13.8 %</td>
<td>23.2 %</td>
</tr>
<tr>
<td>Group C</td>
<td>14.1 %</td>
<td>14.8 %</td>
</tr>
<tr>
<td>Group D</td>
<td>30.8 %</td>
<td>32.8 %</td>
</tr>
</tbody>
</table>
Table 3: Five-year all-cause mortality among spirometry strata within GOLD 2019 ABCD classification

<table>
<thead>
<tr>
<th>GOLD 2019</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spirometry I</td>
<td>3.4 %</td>
<td>9.8 %</td>
<td>16.2 %</td>
<td>5.5 %</td>
</tr>
<tr>
<td>Spirometry II</td>
<td>7 %</td>
<td>14.9 %</td>
<td>8.3 %</td>
<td>22.1 %</td>
</tr>
<tr>
<td>Spirometry III</td>
<td>13 %</td>
<td>23.7 %</td>
<td>17.7 %</td>
<td>32.6 %</td>
</tr>
<tr>
<td>Spirometry IV</td>
<td>16.7 %</td>
<td>39.1 %</td>
<td>29.5 %</td>
<td>46 %</td>
</tr>
</tbody>
</table>
Table 4: Accuracy for predicting mortality of the ABCD groups classifications by GOLD 2015 and GOLD 2019 schemes

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>Sensitivity (% 95 CI)</th>
<th>PPV (% 95 CI)</th>
<th>Indice de Youden (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 2015 group A</td>
<td>11.1 (9.6-12.7)</td>
<td>6.9 (5.9-7.9)</td>
<td>-0.23 (-0.25 – -0.22)</td>
</tr>
<tr>
<td>GOLD 2015 group B</td>
<td>11.6 (10-13,2)</td>
<td>13.3 (11.5-15.1)</td>
<td>-0.06 (-0.08 – -0.04)</td>
</tr>
<tr>
<td>GOLD 2015 group C</td>
<td>14.6 (12.8-16.4)</td>
<td>20.2 (17.9-22.6)</td>
<td>+0.01 (-0.01 – +0.03)</td>
</tr>
<tr>
<td>GOLD 2015 group D</td>
<td>62.5 (60.1-64.9)</td>
<td>29.5 (28-31.1)</td>
<td>+0.28 (+0.25 – +0.31)</td>
</tr>
<tr>
<td>GOLD 2019 group A</td>
<td>19.1 (17.2-21.1)</td>
<td>9.5 (8.4-10.5)</td>
<td>-0.23 (-0.25 – -0.21)</td>
</tr>
<tr>
<td>GOLD 2019 group B</td>
<td>43.6 (41.1-46.1)</td>
<td>21.2 (19.8-22.6)</td>
<td>+0.06 (+0.03 – +0.09)</td>
</tr>
<tr>
<td>GOLD 2019 group C</td>
<td>6.6 (5.3-7.8)</td>
<td>21.7 (18-25.5)</td>
<td>+0.01 (0.0 – +0.02)</td>
</tr>
<tr>
<td>GOLD 2019 group D</td>
<td>30.6 (28.3-32.8)</td>
<td>32.8 (30.4-35.2)</td>
<td>-0.16 (+0.14 – +0.18)</td>
</tr>
</tbody>
</table>

PPV: Positive predictive value. CI: confidence interval
TABLES AND FIGURES:

Table 1: Comparison of demographic and clinical characteristics in 3CIA COPD patients included/excluded in this analysis

Table 2: Mortality risk among COPD patients according to GOLD 2019 and GOLD 2015 classifications

Table 3: Five-year all-cause mortality among spirometry strata within GOLD 2019 ABCD classification

Table 4: Accuracy for predicting mortality of the ABCD groups classifications by GOLD 2015 and GOLD 2019 schemes

Figure 1: Distribution of participants by classification in GOLD 2015 and GOLD 2019

Figure 2: Kaplan-Meier survival curves by GOLD 2015 and GOLD 2019

Figure 3: Kaplan-Meier survival curves by GOLD 2019 and spirometry subgroups (IA-IVD)

Figure 4: Receiver operating curves for all cause mortality at 5 years follow-up
Figure 1: Distribution of participants by classification in GOLD 2015 and GOLD 2019

136x89mm (300 x 300 DPI)
Figure 2: Kaplan-Meier survival curves by GOLD 2015 and GOLD 2019

319x159mm (169 x 169 DPI)
Figure 3: Kaplan-Meier survival curves by GOLD 2019 and spirometry subgroups (IA-IVD)

135x124mm (300 x 300 DPI)
Receiver operating curves for all cause mortality at 5 years follow-up

AUC: area under the curve