External validation and recalculation of the CODEX index in COPD patients:

Almagro, Pere; Turner, Alice; Martinez-Camblor, Pablo; Miravitlles, Marc; Navarro, Annie; Lamprecht, Bernd; Ramírez-García, S.; Kaiser, Bernhard; Casanova, Ciro; Alfageme, Inmaculada; Esteban, Cristobal; de Torres, Juan; Soler-Cataluña, Juan J; Marin, Jose; Celli, Bartolome; Ter Riet, Gerben; Sobradillo, Patricia; Lange, P; Garcia-Aymerich, Judith; Josep, Anto

External validation and recalculation of the CODEX index in COPD patients. A 3CIAplus cohort study.

Journal:	*COPD: Journal Of Chronic Obstructive Pulmonary Disease*
Manuscript ID	COPD-2017-0290.R1
Manuscript Type:	Original Paper
Date Submitted by the Author:	10-May-2018
Complete List of Authors:	Almagro, Pere ; Universitary Hospital Mutua de Terrassa, Multimorbidity Unit. Internal Medicine Department Martinez-Camblor, Pablo; 3. Biomedical Data Science. Geisel School of Medicine at Dartmouth. Hanover. United States, Biomedical Data Science Miravitlles, Marc; Hospital Universitari Vall d'Hebron, Pneumology Rodriguez-Carballeira, Monica; Hospital Universitario Mutua de Terrassa, Internal Medicine Department Navarro, Annie; Hospital Universitario Mutua de Terrassa, Pneumology Lamprecht, Bernd; Paracelsus Medical University Salzburg, University Clinic of Pneumology; General Hospital Linz, Department of Pulmonary Medicine Ramirez Garcia-Luna, Ana Sofia; 8. Facultad de Medicina, Universidad Autónoma de San Luis Potosí, San Luis Potosí, Mexico Kaiser, Berhand; 6. Department of Pulmonary Medicine, Kepler-University-Hospital, Linz, Austria; 7. Faculty of Medicine, Johannes-Kepler-University, Linz, Austria Alfageme, Inmaculada; Hospital Universitario Valme, Seville, Spain , Pneumology Casanova, Ciro; Hospital Nuestra Señora de la Candelaria, Tenerife, Spain Esteban, Cristobal; Hospital Galdakao-Usansolo, Galdakao, Bizkaia, Spain Juan Jose, Soler Cataluña; Hospital Arnau de Vilanova, Valencia, Spain, Pneumology de Torres, Juan P.; Clinica Universidad de Navarra, Pulmonary Celli, Bart; St. Elizabeth's Medical Center, Pulmonary Critical Care Marin, Jose; Hospital Universitario Miguel Servet, Pulmonary ter Riet, Gerben; 17. Department of General Practice, Academic Medical Center-University of Amsterdam (AMC), Amsterdam, The Netherlands Sobradillo, Patricia; Hospital Universitario Araba, sede Txagorritxu, Pneumology

Lange, Peter; Copenhagen University, Department of Public Health; Hvidovre Hospital, Section of Respiratory Medicine
Garcia Aymerich, Judith; ISGlobal, Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain ; Universitat Pompeu Fabra (UPF), Barcelona, Spain
Anto, Josep M; 20. ISGlobal, Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain ; Universitat Pompeu Fabra (UPF), Barcelona, Spain
Turner, Alice; University of Birmingham,
Han, Meilan; University of Michigan, Pulmonary and Critical Care Medicine
Langhammer, Arnulf; Norwegian University of Science and Technology, Department of Public Health and General Practice
Stenberg, Alice; 26. Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health.Baltimore USA;
Leivseth, Linda; 27. Centre for Clinical Documentation and Evaluation, Northern Norway Regional Health Authority, Tromso, Norway
Bakke, Per; 28. Department of Clinical Science, University of Bergen, Bergen, Norway
Johannessen, Ane; Haukeland University Hopsital, Centre for clinical research
Oga, Toru; Kyoto University, Graduate School of Medicine, Respiratory Care and Sleep Control Medicine
Cosio, Borja; Hospital Universitario Son Espases, Respiratory Medicine; Ciber Enfermedades Respiratorias,
Ancoechea, Julio; 32. Servicio de Neumología, Hospital Universitario de la Princesa (IISP), Universidad Autónoma de Madrid, Cátedra UAM-Linde, Madrid, Spain
Echazarreta, Andres; 33. Servicio de Neumonología, Hospital San Juan de Dios de La Plata, Buenos Aires, Argentina
Roche, Nicolas; 34. Service de Pneumologie AP-HP, Hôpitaux Universitaires Paris Centre, France
Burgel, Pierre-Regis; 35. Respiratory Medicine,Paris Descartes University, Paris, France
Sin, Don; University of British Columbia,
Puhan, Milo; 38. Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland
Soriano, Joan; 39. Instituto de Investigación Hospital Universitario de la Princesa (IISP), Universidad Autónoma de Madrid, Cátedra UAM-Linde, Madrid, Spain

Keywords: prognosis, survival, multimorbidity, comorbidity, COPD, CODEX index

TITLE PAGE

External validation and recalculation of the CODEX index in COPD patients. A 3CIAplus cohort study.

Running head: External validation of the CODEX index. 3CIA cohort study

Pere Almagro[1], Pablo Martínez-Camblor[2,3], Marc Miravitlles[4], Mónica Rodríguez Carballeira [1], Annie Navarro[5], Bernd Lamprecht[6,7], Ana S Ramirez-Garcia Luna[8], Bernhard Kaiser[9], Inmaculada Alfageme[10], Ciro Casanova[11], Cristobal Esteban[12], Juan J Soler-Cataluña[13], Juan P de-Torres[14], Bartolome R Celli[15], Jose M Marin[16], Gerben ter Riet[17], Patricia Sobradillo[18], Peter Lange[19], Judith Garcia-Aymerich[20,21,22], Josep M Anto[20,21,22], Alice M Turner[23], MeiLan K Han[24], Arnulf Langhammer[25], Alice Stenberg[26], Linda Leivseth[27], Per Bakke[28], Ane Johannessen[29], Toru Oga[30], Borja Cosío[31], *Julio Ancochea[32], Andres Echazarreta[33]*, Nicolas Roche[34], Pierre-Régis Burgel[35], Don D Sin[36,37], Milo A Puhan[38], Joan B Soriano[39], for the 3CIA collaboration

AUTHOR AFFILIATIONS

1. Multimorbidity Patients Unit, Internal Medicine, Hospital Universitari Mutua de Terrassa, Universitat de Barcelona, Barcelona, Spain
2. Universidad Autónoma de Chile, Chile
3. Geisel School of Medicine at Dartmouth, Hanover, NH, United States.
4. Pneumology Department, Hospital Universitary Vall d'Hebron, CIBER de Enfermedades Respiratorias (CIBERES), Barcelona, Spain
5. Pneumology Service, Hospital Universitari Mútua Terrassa, Barcelona, Spain.
6. Department of Pulmonary Medicine, Kepler-University-Hospital, Linz, Austria
7. 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
10. Hospital Universitario Valme, Seville, Spain
11. Hospital Nuestra Señora de la Candelaria, Tenerife, Spain
12. Hospital Galdakao-Usansolo, Galdakao, Bizkaia, Spain
13. Servicio de Neumología, Hospital Arnau de Vilanova, Valencia, Spain
14. Clinica Universidad de Navarra, Pamplona, Spain
15. Harvard University, Brigham and Women's Hospital, Pulmonary and Critical Care Medicine, 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
19. Section of Social Medicine, Department of Public Health, Copenhagen University, Copenhagen City Heart Study, Frederiksberg Hospital, Frederiksberg, Copenhagen, Denmark
20. ISGlobal, Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain
21. Universitat Pompeu Fabra (UPF), Barcelona, Spain

22. CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain
23. University of Birmingham, Edgbaston, UK,
24. 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
28. Department of Clinical Science, University of Bergen, Bergen, Norway
29. Department of Global Public Health and Primary Care, University of Bergen, 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 Neumología, Hospital Universitario de la Princesa (IISP), Universidad Autónoma de Madrid, Cátedra UAM-Linde, Madrid, Spain
33. Servicio de Neumonología, Hospital San Juan de Dios de La Plata, Buenos Aires, Argentina
34. Service de Pneumologie AP-HP, Hôpitaux Universitaires Paris Centre, France
35. Respiratory Medicine, Paris Descartes University, Paris, France
36. James Hogg Research Centre, University of British Columbia, Vancouver, BC, Canada
37. Division of Respiratory Medicine, Department of Medicine, St Paul's Hospital, Vancouver, BC, Canada
38. Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland
39. Instituto de Investigación Hospital Universitario de la Princesa (IISP), Universidad Autónoma de Madrid, Cátedra UAM-Linde, Madrid, Spain

Corresponding author:

Pere Almagro, Multimorbidity Patients Unit, Internal Medicine Department, Hospital Universitari Mutua de Terrassa, Universitat de Barcelona, Barcelona, Spain

Pza. Dr. Robert nº 5

Terrassa 08221, Barcelona, Spain

e-mail: 19908pam@comb.es

Phone: + 34 93 736 5050

Fax: + 34 93 736 5550

Keywords: prognosis, COPD, mortality, survival, multicomponent index, comorbidities

Abbreviations:

COPD: Chronic Obstructive Pulmonary Disease.

FEV1: Forced Expiratory Volume in the first second.

mMRC: modified dyspnea scale of the Medical Research Council

3CIA: COPD Cohorts Collaborative International Assessment

Post-BD: post bronchodilator

STROBE: STrengthening the Reporting of OBservational studies in Epidemiology.

25%-75% IQR: 25%-75% interquartile range

ROC: receiver operating characteristic curve

AUC: area under the curve

NNE: nearest-neighbor estimator

ESMI: COPD in internal medical services

HR: Hazard Ratio

95% C.I.: 95% Confidence Interval

CODEX index: Comorbidity, Obstruction, Dyspnea, Exacerbations

mCODEX index: modified CODEX index

BODE: Body mass index, Obstruction, Dyspnea, Exercise

BODEX: Body mass index, Obstruction, Dyspnea, Exacerbations

ADO: Age, Dyspnea, Obstruction

HADO: Health, Activity, Dyspnea, Obstruction

DOSE: Dyspnea, Obstruction, Smoking, Obstruction

PEARL: Previous admissions, eMRCD score, Age, Right-sided heart failure, Left-sided heart failure.

Abstract

The CODEX index was developed and validated in patients hospitalized for COPD exacerbation to predict the risk of death and readmission within one year after discharge. Our study aimed to validate the CODEX index in a large external population of COPD patients with variable durations of follow-up. Additionally, we aimed to recalculate the thresholds of the CODEX index using the cut-offs of variables previously suggested in the 3CIA study (mCODEX).

Individual data on 2,755 patients included in the COPD Cohorts Collaborative International Assessment Plus (3CIA+) were explored. A further two cohorts (ESMI AND EGARPOC-2) were added. To validate the CODEX index, the relationship between mortality and the CODEX index was assessed using cumulative/dynamic ROC curves at different follow-up periods, ranging from 3 months up to 10 years. Calibration was performed using univariate and multivariate Cox proportional hazard models and Hosmer-Lemeshow test.

A total of 3,321 (87.8% males) patients were included with a mean ± SD age of 66.9±10.5 years, and a median follow-up of 1,064 days (IQR 25%-75% 426-1643), totalling 11,190 person-years. The CODEX index was statistically associated with mortality in the short- (≤3 months), medium- (≤1 year) and long-term (10 years), with an area under the curve of 0.72, 0.70 and 0.76 respectively. The mCODEX index performed better in the medium-term (<1 year) than the original CODEX, and similarly in the long-term.

In conclusion, CODEX and mCODEX index are good predictors of mortality in patients with COPD, regardless of disease severity or duration of follow-up.

INTRODUCTION

The study of prognosis has been inseparable from medical practice for centuries (1). Some prognostic scores have been widely validated, such as the Karnofsky, Charlson, APACHE and other indices, while others have never been externally validated and their usefulness is debatable (2-4).

The most commonly used variable for evaluating the severity and mortality risk in COPD is postbronchodilator FEV_1, expressed as a percentage of predicted value according to ethnicity, age, sex and height (FEV_1%). Indeed, FEV_1% predicts survival, not only in respiratory patients, but also in cardiovascular disorders and even in the general population (5-8). In COPD, severity of airflow limitation has been classified according to different thresholds, which have changed over time and which have been endorsed by different scientific societies (9). To date, the most widely accepted classification, for the sake of simplicity and its broad implementation, is the staging proposed by the Global Obstructive Lung Disease Initiative (GOLD) to evaluate with the degree of postbronchodilator FEV_1% expressed as percentage of their predicted value (≥80%; 50-79%; 30-49%; ≤ 29% for mild, moderate, severe and very severe airflow limitation, respectively), although these suggested cut-offs are slightly different from those validated for mortality in prospective cohort studies (namely, ≥85%; 55-84%; 35-54%; ≤ 34%) (7-8). The second variable in importance for staging COPD is dyspnea, often measured with the modified scale of the Medical Research Council (mMRC), which in patients with more severe obstruction is an even better predictor of mortality than FEV_1% alone (10,11). These two variables were historically the first prognostic variables recognized in COPD (12,13). Additionally, the combination of these two

variables—airflow limitation and dyspnea—is the cornerstone of most of the multicomponent indices developed for COPD prognosis including BODE, BODEx, ADO, DOSE and HADO (14-18). There are other important variables to evaluate prognosis in COPD, such as sub-phenotypes and the risk of exacerbations or comorbidities, among others (15,19).

The CODEX index was developed and validated in patients hospitalized for an acute exacerbation of COPD with the objective of evaluating the prognosis in the short- (3-months) and medium-term (1-year) for mortality, hospital readmission or their combination (19). Later, it was revalidated in a small cohort of outpatients with severe COPD for mortality and exacerbations, and more recently exclusively for mortality in another retrospective study performed in a cohort of ambulatory patients (20,21). Finally, CODEX index was compared with other index for the combination of 90-day mortality and readmissions after a hospitalization for COPD exacerbation (22). However, to date formal validation of its accuracy across a variety of COPD patient cohorts, and different follow-up periods has not been done.

Our main objective was the validation and recalculation of the CODEX index for mortality, in a broader cohort of COPD patients, recruited either at the general population, outpatient or hospital levels, with different stages of severity and with varying periods of follow-up ranging from 3 months up to 10 years.

METHODS

We obtained individual pooled data from 26 cohort studies from 8 countries, all previously published, and from the COPD Cohorts Collaborative International Assessment (3CIA) consortium database, later expanded to 3CIA+ (7). Briefly, the 3CIA database contains individual data from 16,332 COPD patients, at the outpatient and hospital levels, spirometrically confirmed by a post-BD ratio $FEV_1/FVC < 0.7$, according to the GOLD criteria (7). The 3CIA+ cohort has follow-up data and information on age, sex, pre-and post-BD FEV_1, mMRC dyspnea scale and mortality, among others. Only in a number of 3CIA+ cohorts were data of comorbidity measured with Charlson index and number of hospitalizations in the previous year available. For the current study, we selected exclusively those cohorts in which Charlson index and number of severe exacerbations in the previous year were available in the database, since both are required to calculate the CODEX index. CODEX index is composed of the combination of FEV_1%, dyspnea and number of severe COPD exacerbations in the previous year, stratified according to the BODE and BODEX thresholds, but replacing body mass index with the original age-adjusted Charlson index, the most widely recognized prognostic index of comorbidity (3). Severe exacerbations were defined as those that required hospitalization or emergency room visits (6,15). (Table 1)

The original, age-adjusted Charlson index is a standard scale with 15 chronic diseases graded for severity, including COPD, in which one point is added to the total score of comorbidity for each decade of life over the age of 50 years (3). To calculate the CODEX index, age-adjusted Charlson was stratified in tertiles, while the stratification of %predicted FEV_1 and dyspnea was the same

as is used in both the BODE and BODEX indices and the thresholds for exacerbations were those used in the BODEX index. In the present study, we attempted to recalculate the CODEX index (mCODEX) by replacing the original CODEX thresholds for FEV_1% and dyspnea (mMRC) with the previously suggested cut-offs based on survival prediction analysis in 3CIA and ADO, which are ≥85%; 55-84%; 35-54%; <34% for FEV_1% and 0-1; 2; 3 and 4 for dyspnea (7,8,16). Thus, possible scores for the CODEX and mCODEX indices range from 0 to 10 points (19). (Table 1)

Two cohorts not previously included in 3CIA+, namely ESMI and EGARPOC-2, were added. Since the CODEX index was developed using the data of the ESMI study, and in order to rule out a possible bias, a previous subanalysis was carried out to assess the AUCs of the ESMI study vs. the rest of the cohorts. ESMI and EGARPOC-2 contain all the variables included in 3CIA+, plus the Charlson index and follow-up for mortality (20,23). All the original cohort studies were approved by the respective ethics committees and all patients gave their informed consent. For the development of the present study the STROBE recommendations for observational cohort studies were followed (24).

Statistical analysis

Categorical variables were expressed as absolute frequencies and percentages, and continuous variables were summarized as mean and standard deviation, or median and 25-75% interquartile range (25%-75% IQR), wherever appropriate. Comparisons among means were made using the Student t-test or Mann-Whitney test according to normality assumptions. For validation purposes, we used the cumulative/dynamic area under the receiver operating characteristic curve (ROC) to express the ability of both CODEX and

mCODEX indices to predict all-cause mortality for short-term (0 to 3-months), medium-term (3 to 12-months) and long-term follow-up (1-10-years). Dynamic cumulative ROC curves were selected as they are considered the most appropriate method when the considered outcome (in our case mortality) is a time-dependent variable. We used the nearest-neighbor estimator (NNE) proposed by Heagerty, Lumley and Pepe to estimate the AUC, and the naïve bootstrap procedure to estimate 95% confidence intervals (95% CI) (25). Detailed methodology is available elsewhere (26). Calibration was performed with univariate and multivariate Cox proportional hazard models and Hosmer-Lemeshow test. Mortality curves were calculated using the Kaplan-Meier estimator. Univariate Cox proportional hazard models were used to study the crude effect of the CODEX and mCODEX tertiles on survival. A random-effect multivariable Cox proportional hazard model including sex and age was used to study the adjusted effect of the CODEX and mCODEX tertiles on survival. In order to deal with the sample heterogeneity, a gaussian frailty term was added to both models, which were stratified by cohort (25,27). Finally, we explored the reliability of CODEX and mCODEX in different subgroups stratified by sex, age, FEV1(%) and dyspnea. For all analyses, we used free software R (www.r-project.org). In particular, package survivalROC and survival were used to compute the AUC indices and develop the time-dependent analysis. A two-sided p value below 0.05 was considered statistically significant.

Results

Twelve of the 26 cohorts included in the 3CIA contain in their protocol the data necessary to calculate the CODEX index, specifically Charlson index and the number of exacerbations in the previous year, totaling 3,142 patients. Of these 3,142 patients initially included, 363 were excluded due to a lack of individual data to calculate CODEX index and 24 for missing follow-up.

These excluded patients had better lung function (mean FEV_1%: 56.2 % vs. 51.6%; p <0.001) and were more often male [394/2,785 (14.3%) vs. 32/387 (8.3%); p =0.002), with no differences on the dyspnea scale (median 2.72 vs 2.40; p=0.381) or age (mean 66.8 vs. 67.2 years; p=0.415). A total of 566 patients from the ESMI and EGARPOC cohorts were added to the study. (Figure 1) In all included patients, data to calculate the CODEX index were available, and hence we did not impute missing data.

The AUC for ESMI study compared with the global cohort was nearly identical, and therefore we decided to maintain it in both the validation and recalibration cohort. (Figure E1 Supplementary material)

In sum, a total of 3,321 patients were included in the study, with a mean age of 66.9 (SD 10.5) years, and 87.8% were males. The median follow-up was 1,064 days with an interquartile range (IQR) 25-75% of 426 to 1,643 days, totaling an experience of 11,990 person-years. The main characteristics of the studied population are presented in Table 2, while the distribution of CODEX and mCODEX indices is detailed in Figure 2. A total of 1,175 (35.4%) patients were included after a hospitalization for exacerbation of COPD, while 2,146 (64.6%) were selected in ambulatory settings. Hospitalized patients were older [72 (9.4)

vs. 64.1 (10) years; p<0.001], with higher scores in the Charlson index [6.8 (2.6) vs. 4.3 (2.2); p<0.001], lower values of FEV_1% [46 (17.1) vs. 53.9 (19.8); p<0.001], higher scores in the mMRC dyspnea scale [median 3 (IQR 75%:3-4) vs. 2 (IQR 75%: 2-3); p<0.001], and without differences for gender and severe exacerbations in the previous year. Both CODEX [5.4 (2) vs. 3.8 (2.2); p<0.001] and mCODEX [5.7 (1.7) vs. 4.3 (1.9); p<0.001] showed higher scores in hospitalized patients.

The overall observed mortality ranged from 6.3% (1-year) and 20% (3-years) to 58% at 10-years. The AUC for CODEX and mortality ranged from 0.72 (95% CI: 0.60-0.77) at 3 months to 0.76 (95% CI:0.70-0.79) at 10 years, and between 0.73 (95% C.I:0.67-0.78) at 3 months and 0.75 (95% C.I.: 0.69-0.79) at 10 years in the mCODEX. The mCODEX performed slightly better, although without statistically significant differences, in the short (3-months) and medium term (1-year), and similarly in the rest of the follow-up. (Table 3) Both models were well calibrated according to the Hosmer-Lemeshow test. (Table E-1, Supplementary material)

Table 4 shows the hazard ratios (HR) and their respective 95% confidence intervals for crude and adjusted survival, one in which just the covariate of interest was included, and another random-effect one adjusted for age, sex and cohort. Other covariables were not included since the CODEX and mCODEX indices already contained comorbidity, obstruction, dyspnea and previous exacerbations. The hazard ratio of the highest and lowest tertiles was 4.59 (95% C.I.:3.93-4.74) and 5.02 (95% C.I.:4.17-6.05) for CODEX and mCODEX in the unadjusted model and 3.93 (95% C.I.:3.27-4.44) and 4.31 (95% C.I.: 5.54-

5.26), respectively, in the adjusted model. Figure 3 shows the Kaplan-Meier estimates for the survival curves stratified by tertiles of CODEX and mCODEX.

Table 5 presents the sensitivity analysis for subgroups stratified by age, gender, FEV_1% and dyspnea at clinically relevant cut-offs and different follow-up periods, graphically displayed in Figures 4A and 4B. In these analyses, CODEX and mCODEX performed well, confirming that both indices are useful in the different population subgroups, and highlighting the high AUC in the younger patients in the short term (0.95 and 0.84 at 3 and 6 months, respectively) for CODEX and mCODEX. Inversely, the utility of both indices in women in the short and medium term (<3-years) was lower for CODEX than for mCODEX (0.66 and 0.64 vs. 0.7 and 0.71) at 3 and 12 months, respectively. Of note, the predictive capacity of CODEX and mCODEX for mortality in the short and medium term was higher in outpatients (Table 5. Figures 4A and 4B).

Discussion

Our study confirms the utility of the CODEX index to predict mortality in a large set of COPD patients. The study design–a pooled-analysis of individual patient-data from several cohorts–sample size and the different degrees of severity of the patients in the different cohorts maximize its high external validity. Importantly, these replication results were consistent in sensitivity analyses and across different COPD sub-populations.

Additionally, we recalculated the original CODEX index with different thresholds for FEV_1% and dyspnea, previously obtained from the 3CIA cohort for survival prediction. Of note, these new cut-offs were similar to those found in a large-

scale international validation study conducted in 10 cohorts including 13,914 patients in the validation of the ADO index (7,8,16).

In the past few years, a number of multicomponent prognostic indices have been developed to predict progression and outcomes in COPD patients (29). These scores were created by the combination of different variables with diverse thresholds, but their usefulness and reproducibility are highly variable. Some of them were created basically with statistical criteria, for others calculation is complex, some were based on literature reviews and most have never been externally validated (4,30,31).

To date, the most frequently referenced multicomponent prognostic scale in COPD is the BODE index, originally developed in ambulatory patients with a low burden of comorbidity, and subsequently validated in other populations (14,32). The BODE index has also shown good sensitivity in detecting changes in the progression and outcomes of COPD, such as exacerbations, pulmonary rehabilitation, lung volume reduction techniques and lung transplantation, among others (33-36). Following BODE, several other multicomponent indices have been developed and validated in different populations and with diverse objectives. The DECAF score was developed and later validated to predict in-hospital mortality in patients with COPD exacerbations, while the DOSE index was developed in primary care to evaluate the risk of exacerbations; it was later related with mortality (17,37-40). The ADO index has been shown to have a high discriminatory power (AUC 0.85 and 0.73 for the updated cohort and derivation cohort respectively) and calibration for 3-year mortality, although some authors feel that the weight of age in ADO may be excessive (16,41). A modification of BODE is the BODEx index, which replaces the 6-minute walking

test with severe exacerbations in the previous year, and which has a similar 3-year predictive value (15). More recently, a new tool (PEARL score) has been developed to predict the risk of death or readmission at 90 days after hospital discharge. This study was performed in 2,417 patients included in the DECAF study who survived to discharge. PEARL score was superior to ADO, BODEX, and DOSE in all three cohorts, and to CODEX within the internal and external validation cohorts, but similar in the internal validation cohort (AUC for CODEX=0.66 vs PEARL 0.68) (22).

All these indices have been externally validated and even directly compared in others cohorts (42,43). External validation is essential to determine the reproducibility of prediction models and to explore whether predictions obtained by the model are valid in other populations (44,45).

CODEX index was originally developed in a multicenter cohort of patients hospitalized for COPD exacerbation, and externally validated in the original publication in three other similar cohorts (19). Later, it was revalidated in two cohorts of ambulatory patients with good discrimination (AUC: 0.80) (20,21). This is in accordance with the data of the present study that show a higher predictive capacity in outpatients, retaining similar values of AUC to those observed in the original study for hospitalized patients.

CODEX has several strengths and some weaknesses. Among the strengths are that its variables are easy to collect, and all closely and clinically related to the prognosis of these patients, especially the impact of comorbidity measured with the original age-adapted Charlson index (46). Additionally, CODEX was superior to BODEX, DOSE and updated ADO in patients hospitalized for COPD

in the short and medium term (19). However, to date few external validations are available, and its performance in the longer term and in other populations has not been studied. Our results confirm the ability of the CODEX index to predict mortality in a large sample of patients and across diverse COPD populations, with different degrees of severity. In COPD multicomponent indices are useful to compare the severity of the disease among different populations, and to enhance informed decision-making with the patient. However, the individual prognosis in COPD is highly variable and these models can assist clinicians but do not replace clinical judgment. (47)

Additionally, we attempted to improve CODEX by modifying the cut-offs for FEV_1% and dyspnea with those suggested previously in 3CIA, which are very similar to those proposed by Puhan et al. in the updated ADO (7,8,16). Updating a predictive model is often desirable, especially when the model is applied in settings that differ from that of the development sample or when investigating new thresholds of included variables if there are new data that suggest an improvement of its predictive capacity (44,45). This new mCODEX performed slightly better, in the short term (3-months) and medium term (1-year), and similarly in longer follow-up times. The most plausible explanation for the small differences found between CODEX and mCODEX is the small differences in the thresholds selected, confirming the reliability of the cut-offs previously selected in the BODE and BODEx index. Although these differences could have been maximized with statistical criteria their clinical applicability would be more doubtful.

Our study has several limitations. First, mortality was the only outcome assessed, while in the original publication CODEX index was related to three

outcomes, namely risk of mortality, hospital admissions and their combination. Regrettably we do not have sufficient, consistent data on 3CIA+ in hospital admissions after inclusion of patients. In this sense the present study is similar to the previous publications of prognostic indices in COPD (BODE, BODEX, ADO…) that have mortality as the exclusive outcome (14-16). Second, our study had a clear predominance of men. Whereas in the 3CIA+ study the percentage of women was 31%, in our study after the exclusion of patients with missing data for Charlson index and previous severe exacerbations, this percentage dropped to 12%. Nevertheless, the number of women (404) was sufficient to detect differences between gender groups above or equal to 0.15 standard deviation at the standard statistical power of 80%. The rest of the differences between included and excluded cohorts are small; patients without Charlson index were slightly older with a similar number of severe exacerbations in the previous year and similar level of dyspnea. Third, there was great variability in the severity and outcomes across the individual studies included. However, this might also be considered a strength because it enabled inclusion of patients with a full range of COPD disease severity.

To conclude, our study confirms the utility of the CODEX index for mortality prediction in a large cohort of COPD patients. Its reliability was demonstrated across diverse COPD populations, in all subgroups analyzed and in different periods of follow-up.

Declaration of interest

The authors declare that they have no conflict of interests with the present manuscript.

Role of the funding source

We received no specific funding for this work. PA, PMC and JBS accept final responsibility for the integrity of the work as a whole. They had full access to all data in the study, and they take responsibility for the accuracy of all the analyses.

Acknowledgments: The COCOMICS study was funded in part by a grant from the Spanish Society of Pneumology and Thoracic surgery (SEPAR) coded with the number 057/12.SEPAR 2013. We thank Tom Yohannan (professional medical copy-editor) for his editorial assistance.

Conception and design: PA, PMC, MRC, AN, JBS. Analysis and interpretation: PA, PMC, MRC, AN, JBS. Drafting the manuscript for important intellectual content: PA, PMC, MM, MRC, AN, BL, ASR, BK, IA, CC, CE, JJSC, JPT, BRC, JMM, GTR, PS, PL, JGA, JMA, AMT, MLKH, AL, TO, BC, JA, AE, NR, PRB, DDS, MAP, JBS.

References:

1. Charles Joseph Singer EAU. A short history of medicine. Second edition. Oxford University press; 1962.

2. Evans C MM. Prognostic uncertainty in terminal care: can the Karnofsky index help? Lancet. 1985;8439:1204–6.

3. Charlson ME, Pompei P, Ales KL MC. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.

4. Salpeter SR, Luo EJ, Malter DS, Stuart B. Systematic review of noncancer presentations with a median survival of 6 months or less. Am J Med. 2012;125:512.e1-512.e16.

5. Schünemann HJ, Dorn J, Grant BJ, Winkelstein W Jr TM. Pulmonary function is a long-term predictor of mortality in the general population: 29-year follow-up of the Buffalo Health Study. Chest. 2000;118(3):656–64.

6. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J,et al. Global Strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 Report. GOLD Executive Summary. Am J Respir Crit Care Med. 2017;195 (5):557-582.

7. Soriano JB, Lamprecht B, Ramírez AS, Martinez-Camblor P, Kaiser B, Alfageme I,et al. Mortality prediction in chronic obstructive pulmonary disease comparing the GOLD 2007 and 2011 staging systems: A pooled analysis of individual patient data. Lancet Respir Med. 2015;3(6):443–50.

8. Almagro P, Martinez-Camblor P, Soriano JB, Marin JM, Alfageme I, Casanova C,et al. Finding the best thresholds of FEV1and dyspnea to predict 5-year survival in COPD patients: The COCOMICS study. PLoS One. 2014;9(2):1–7.

9.-Atsou K, Chouaid C, Hejblum G. Variability of the chronic obstructive pulmonary disease key epidemiological data in Europe: systematic review. BMC Med. 2011;9:7.

10.- Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax. 1999;54(7):581–6.

11. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. Chest. 2002;121(5):1434–40.

12.-Jones NL, Burrows B, Fletcher CM. Serial studies of 100 patients with chronic airway obstruction in London and Chicago. Thorax. 1967 ;22(4):327-35.

13.-Renzetti AD Jr. Prognosis in chronic obstructive pulmonary disease. Med Clin North Am.1967;51:363-71.

14. Celli BR, Cote CG, Marin JM, Montes de Oca M, Mendez RA, Pinto Plata V, et al. The body mass index, airflow obstruction, dyspnea and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350(10):1005–12.

15. Soler-Cataluña JJ, Martínez-García MÁ, Sánchez LS, Tordera MP, Sánchez PR. Severe exacerbations and BODE index: Two independent risk factors for death in male COPD patients. Respir Med. 2009;103(5):692–9.

16. Puhan MA, Hansel NN, Sobradillo P, Enright P, Lange P, Hickson D, et al. Large-scale international validation of the ADO index in subjects with COPD: an individual subject data analysis of 10 cohorts. BMJ Open. 2012;2:2012–152.

17. Jones RC, Donaldson GC, Chavannes NH, Kida K, Dickson-Spillmann M, Harding S, et al. Derivation and validation of a composite index of severity in chronic obstructive pulmonary disease: The DOSE index. Am J Respir Crit Care Med. 2009;180(12):1189–95.

18. Esteban C, Quintana JM, Moraza J, Aburto M, Aguirre U, Aguirregomoscorta JI, et al. BODE-Index vs HADO-score in chronic obstructive pulmonary disease: Which one to use in general practice? BMC Med. 2010;8:28.

19.- Almagro P, Soriano JB, Cabrera FJ, Boixeda R, Alonso-Ortiz MB, Barreiro B,et al. Short- and medium-term prognosis in patients hospitalized for COPD exacerbation: the CODEX index. Chest. 2014;145(5):972–80.

20.-Navarro A, Costa R, Rodriguez-Carballeira M, Yun S, Lapuente A, Barrera A, et al. Prognostic assessment of mortality and hospitalizations of outpatients with advanced chronic obstructive pulmonary disease. Usefulness of the CODEX index. Rev Clín Esp. 2015;215(8):431–8.

21.-Golpe R, Suárez-Valor M, Veres-Racamonde A, Cano-Jiménez E, Martín-Robles I, Sanjuán-López P, Pérez-de-Llano L. Octogenarian patients with

chronic obstructive pulmonary disease: Characteristics and usefulness of prognostic indexes. Med Clin (Barc). [Epub ahead of print]

22.-Echevarria C, Steer J, Heslop-Marshall K, Stenton SC, Hickey PM, Hughes R, et al. The PEARL score predicts 90-day readmission or death after hospitalisation for acute exacerbation of COPD. Thorax. 2017 72(8):686-693.

23. Almagro P, Cabrera FJ, Diez J, Boixeda R, Alonso Ortiz MB, Murio C, et al. Comorbidities and short-term prognosis in patients hospitalized for acute exacerbation of COPD: the EPOC en Servicios de medicina interna (ESMI) study. Chest. 2012;142(5):1126-33.

24.- von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453-7.

25.- Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. Biometrics. 2000;56(2):337-44.

26.- Martínez-Camblor P, Bayón GF, Pérez-Fernández S. Cumulative/dynamic ROC curve estimation. Journal of Statistical Computation and Simulation. 2016;86: 3582-3594.

27.- O'Quigley J, Stare J. Proportional hazards models with frailties and random effects. Stat Med. 2002;21(21):3219-33.

28.- Steyerberg EW. Prognosis Research Strategy (PROGRESS) 3: prognostic model research. PLoS Med. 2013;10(2):e1001381.

29.- Dijk WD, Bemt Lv, Haak-Rongen Sv, Bischoff E, Weel Cv, Veen JC, et al. Multidimensional prognostic indices for use in COPD patient care. A systematic review. Respir Res. 2011;12:151.

30.- Connors AF Jr, Dawson NV, Thomas C, Harrell FE Jr, Desbiens N, Fulkerson WJ, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). Am J Respir Crit Care Med. 1996;154(4):959-67.

31.- Mannino D, Sin DD. Development and validation of a prognostic index for health outcomes in chronic obstructive pulmonary disease. Arch Intern Med. 2008;168(1):71-9.

32.- Sanjaume M, Almagro P, Rodríguez-Carballeira M, Barreiro B, Heredia JL, Garau J. Post-hospital mortality in patients re-admitted due to COPD. Utility of BODE index. Rev Clin Esp. 2009;209(8):364-70.

33.- Cote CG, Dordelly LJ, Celli BR. Impact of COPD exacerbations on patient-centered outcomes. Chest. 2007;131:696-704.

34.-Güell MR, Cejudo P, Ortega F, Puy MC, Rodríguez-Trigo G, Pijoan JI, et al. Benefits of long-term pulmonary rehabilitation maintenance program in severe COPD Patients: 3 year follow-up. Am J Respir Crit Care Med. 2017;195(5):622-629.

35.- Imfeld S, Bloch KE, Weder W, Russi EW. The BODE index after lung volume reduction surgery correlates with survival. Chest. 2006;129(4):873-8.

36.- Lahzami S, Bridevaux PO, Soccal PM, Wellinger J, Robert JH, Ris HB, et al. Survival impact of lung transplantation for COPD. Eur Respir J. 2010 ;36(1):74-80.

37.- Steer J, Gibson J, Bourke SC. The DECAF Score: predicting hospital mortality in exacerbations of chronic obstructive pulmonary disease. Thorax. 2012;67(11):970-6.

38.- Echevarria C, Steer J, Heslop-Marshall K, et al. Validation of the DECAF score to predict hospital mortality in acute exacerbations of COPD. Thorax. 2016;71(2):133-40.

39.- Jones RC, Price D, Chavannes NH, , Lee AJ, Hyland ME, Ställberg B,et al. Multi-component assessment of chronic obstructive pulmonary disease: an evaluation of the ADO and DOSE indices and the global obstructive lung disease categories in international primary care data sets. NPJ Prim Care Respir Med. 2016;26:16010.

40.- Sundh J, Janson C, Lisspers K, Ställberg B, Montgomery S. The Dyspnea, Obstruction, Smoking, Exacerbation (DOSE) index is predictive of mortality in COPD. Prim Care Respir J. 2012;21(3):295-301.

41.- Celli BR, Marin JM, Cote CG, Aguirre A, Macario CC. Prognostic assessment of patients with COPD. Lancet. 2009;374(9705):1885.

42.- Marin JM, Alfageme I, Almagro P, Casanova C, Esteban C, Soler-Cataluña JJ, et al. Multicomponent indices to predict survival in COPD: the COCOMICS study. Eur Respir J. 2013;42(2):323-32.

43.-Ou CY, Chen CZ, Yu CH, Shiu CH, Hsiue TR. Discriminative and predictive properties of multidimensional prognostic indices of chronic obstructive pulmonary disease: a validation study in Taiwanese patients. Respirology. 2014 ;19(5):694-9.

44.- Collins GS, de Groot JA, Dutton S, Omar O, Shanyinde M, Tajar A, et al. External validation of multivariable prediction models: a systematic review of methodological conduct and reporting. BMC Med Res Methodol. 2014;14:40.

45.- Nieboer D, van der Ploeg T, Steyerberg EW. Assessing discriminative performance at external validation of clinical prediction models. PLoS One. 2016;11(2):e0148820.

46.- Donaldson GC, Wedzicha JA. The CODEX index: a collection or digest of laws: a code. Chest. 2014;145 (5):934-5.

47.- Almagro P, Yun S, Sangil A, Rodríguez-Carballeira M, Marine M, Landete P, Soler-Cataluña JJ, Soriano JB, Miravitlles M. Palliative care and prognosis in COPD: a systematic review with a validation cohort.Int J Chron Obstruct Pulmon Dis. 2017 ;12:1721-1729.

Figure footnotes

Figure 1

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) flowchart of participants and causes of exclusion.

Figure 2

Distribution of CODEX and mCODEX in the study population. N= number of subjects for each point of CODEX and mCODEX.

Figure 3

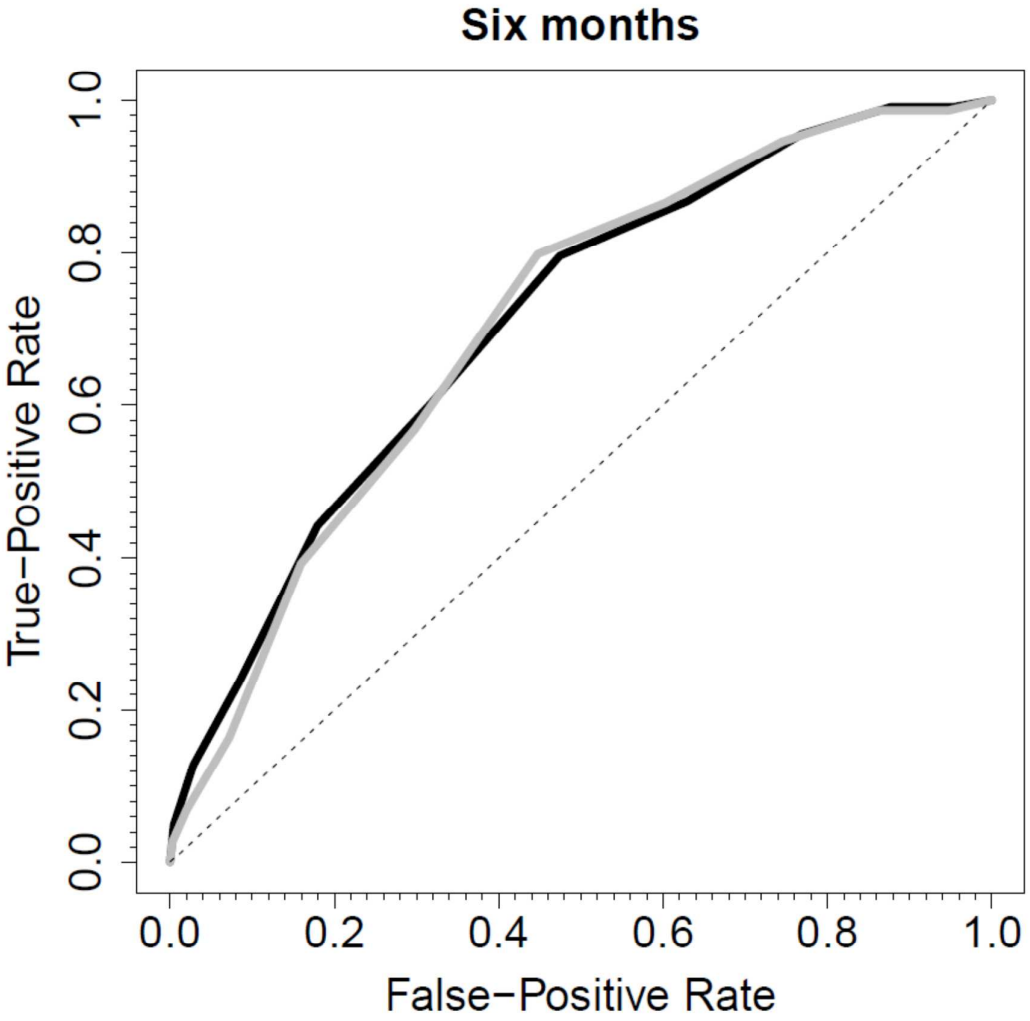
Kaplan-Meier curves for mortality stratified in tertiles for CODEX and mCODEX. The gray shading represents the 95% confidence intervals.

Figure 4 a) and b).

AUCs and 95% confidence intervals for mortality, stratified by relevant subgroups for a) CODEX, and b) mCODEX, and different periods of follow-up.

Supplementary material

Figure E1 Supplementary material



Comparative/Dynamics AUCs at 6-months' mortality, ESMI (gray line), vs. total cohorts (black line)

Table E1.

	CODEX	m-CODEX
	Hosmer-Lemeshow test	
	p	p
3 months	0.06	0.07
12 months	0.48	021
3 years	0.83	0.79
5 years	0.48	0.7
10 years	0.53	0.76

Calibration for CODEX and mCODEX during different follow-up periods, performed with Hosmer-Lemeshow test. In this test values greater than 0.05 indicate good calibration of the model.

Table 1

Variables and thresholds to estimate the CODEX and mCODEX indices

CODEX	POINTS	0	1	2	3
	Charlson index *	0-4	5-7	≥8	
	FEV1 (%) PBD	≥65	50-64	36-49	≤35
	Dyspnea (mMRC)	0-1	2	3	4
	Severe exacerbations	0	1-2	≥3	
mCODEX	POINTS	0	1	2	3
	Charlson index *	0-4	5-7	≥8	
	FEV1 (%) PBD	≥85	55-84	35-54	≤35
	Dyspnea (mMRC)	0	1-2	3	4
	Severe exacerbations	0	1-2	≥3	

The Charlson index is adjusted for age, according to the original description, adding 1 point for each decade after 50 years and preserving 1 point for COPD.

Table 2

Demographic and clinical characteristics of the study participants

	Descriptive
Patient-years	11,183.19
Age, mean±sd	66.9±10.5
Gender, male, n (%)	2,917 (87.8)
BMI, mean±sd	27.6±5.1
FEV1 (ml), mean±sd	1.41±0.62
FVC (ml), mean±sd	3.26±1.3
%FEV1%, mean±sd	51.1±19.2
GOLD classification	
Mild	293 (8.8)
Moderate	1,299 (39.1)
Severe	1,018 (30.7)
Very severe	711 (21.4)
Dyspnea (mMRC)	
0	14 (0.4)
1	565 (17)
2	1007 (30.3)
3	1043 (31.4)
4	692 (20.8)
Charlson index, mean±sd	2.9 (2.07)
Exacerbations*, mean±sd	0.99±1.72
Smoking history	
Former	2,472 (74.4)
Current	710 (21.4)
Non-smoker	79 (2.4)
Missing	60 (1.8)
Pack-years, mean±sd	45.2±31.4
6MWT, mean±sd	374±128
Setting of inclusion Hospitalized	1,175 (35.4%) 2,146 (64.6%)

Outpatients	

Exacerbations*= number of severe exacerbations in the previous year.

Table 3

Cumulative/dynamic area under the ROC curves, and 95% confidence interval at different periods of follow-up.

	Area under dynamic cumulative ROC curves (95% C.I.)	
	CODEX	mCODEX
3 months	0.716 (0.655; 0.774)	0.729 (0.670; 0.783)
6 months	0.710 (0.663; 0.755)	0.716 (0.670; 0.760)
1 year	0.696 (0.662; 0.730)	0.709 (0.667; 0.733)
5 years	0.706 (0.679; 0.731)	0.710 (0.683; 0.734)
10 years	0.757 (0.702; 0.789)	0.753 (0.693; 0.786)

95% C.I.= 95 Confidence Interval

Table 4. Hazard ratios (HR) and their respective 95% confidence intervals for crude and adjusted survival

	CODEX		mCODEX	
	Crude	**Adjusted**	**Crude**	**Adjusted**
Tertile 1	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]
Tertile 2	2.41 (2.00; 2.91)	2.09 (1.72; 2.53)	2.84 (2.41; 3.34)	2.49 (2.10; 2.93)
Tertile 3	4.59 (3.83; 5.40)	3.93 (3.27; 4.74)	5.02 (4.17; 6.05)	4.31 (5.54; 5.26)

[Ref.]=Reference. Adjusted for sex, age, and frailty model for cohort.

Table 5. Sensitivity analysis for subgroups and mortality, at different follow-up periods.

		Area under C/D ROC curve (95% CI)	
		CODEX	mCODEX
Age			
< 60	**3 months**	0.950 (0.927; 0.981)	0.952 (0.931; 0.982)
N=857	**6 months**	0.838 (0.704; 0.945)	0.823 (0.650; 0.949)
	1 year	0.718 (0.586; 0.840)	0.720 (0.584; 0.838)
	5 years	0.674 (0.610; 0.733)	0.695 (0.635; 0.753)
	10 years	0.682 (0.593; 0.757)	0.683 (0.603; 0.757)
61-70	**3 months**	0.712 (0.570; 0.831)	0.703 (0.557; 0.826)
N=1143	**6 months**	0.720 (0.635; 0.800)	0.709 (0.623; 0.790)
	1 year	0.706 (0.640; 0.769)	0.701 (0.633; 0.764)
	5 years	0.721 (0.677; 0.764)	0.716 (0.672; 0.759)
	10 years	0.767 (0.708; 0.820)	0.745 (0.685; 0.799)
+70	**3 months**	0.632 (0.549; 0.711)	0.647 (0.571; 0.719)
N=1321	**6 months**	0.631 (0.561; 0.697)	0.645 (0.577; 0.719)
	1 year	0.628 (0.580; 0.674)	0.631 (0.583; 0.677)
	5 years	0.641 (0.595; 0.688)	0.637 (0.589; 0.683)
	10 years	0.675 (0.499; 0.748)	0.644 (0.466; 0.762)
Gender			
Men	**3 months**	0.719 (0.659; 0.776)	0.729 (0.674; 0.784)
N=2917	**6 months**	0.708 (0.659; 0.754)	0.714 (0.667; 0.759)
	1 year	0.695 (0.661; 0.730)	0.700 (0.666; 0.734)
	5 years	0.704 (0.676; 0.732)	0.708 (0.682; 0.736)
	10 years	0.758 (0.699; 0.789)	0.752 (0.694; 0.784)
Women	**3 months**	0.659 (0.332; 0.967)	0.695 (0.402; 0.967)
N=404	**6 months**	0.694 (0.463; 0.901)	0.712 (0.497; 0.900)
	1 year	0.642 (0.434; 0.827)	0.653 (0.455; 0.826)
	5 years	0.689 (0.606; 0.763)	0.698 (0.612; 0.772)
	10 years	0.664 (0.540; 0.794)	0.730 (0.506; 0.856)
Setting of Inclusion			
Outpatients			
N=2196	**3 months**	0.750 (0.671; 0.822)	0.766 (0.689; 0.835)
	6 months	0.729 (0.668; 0.786)	0.732 (0.669; 0.790)
	1 year	0.722 (0.667; 0.756)	0.715 (0.671; 0.735)
	5 years	0.699 (0.667; 0.733)	0.703 (0.671; 0.757)
Hospitalized			
N=1175	**10 years**	0.737 (0.675; 0.779)	0.729 (0.668; 0.771)
	3 months	0.653 (0.550; 0.755)	0.664 (0.566; 0.759)
	6 months	0.678 (0.600; 0.752)	0.684 (0.610; 0.757)
	1 year	0.658 (0.604; 0.712)	0.660 (0.606; 0.713)
	5 years	0.691 (0.644; 0.737)	0.693 (0.647; 0.737)
	10 years	0.747 (0.677; 0.814)	0.741 (0.669; 0.808)

		Area under C/D ROC curve (95% CI)	
		CODEX	mCODEX
%FEV1			
< 40%	3 months	0.628 (0.519; 0.733)	0.628 (0.521; 0.731)
N=1107	6 months	0.629 (0.548; 0.705)	0.628 (0.547; 0.705)
	1 year	0.623 (0.563; 0.680)	0.626 (0.567; 0.683)
	5 years	0.615 (0.564; 0.665)	0.607 (0.555; 0.659)
	10 years	0.704 (0.528; 0.782)	0.701 (0.531; 0.780)
40%-60%	3 months	0.788 (0.675; 0.883)	0.798 (0.697; 0.881)
N=1174	6 months	0.716 (0.627; 0.796)	0.736 (0.647; 0.815)
	1 year	0.691(0.629; 0.749)	0.703 (0.641; 0.757)
	5 years	0.653 (0.608; 0.699)	0.670 (0.626; 0.715)
	10 years	0.658 (0.584; 0.728)	0.645 (0.572; 0.713)
+60%	3 months	0.755 (0.590; 0.885)	0.783 (0.624; 0.900)
N=987	6 months	0.731 (0.601; 0.843)	0.743 (0.618; 0.852)
	1 year	0.720 (0.618; 0.812)	0.714 (0.619; 0.799)
	5 years	0.659 (0.598 0.717)	0.672 (0.608; 0.731)
	10 years	0.680 (0.611; 0.738)	0.683 (0.621; 0.743)
mMRC			
0-1	3 months	0.709 (0.516; 0.858)	0.733 (0.516; 0.882)
N=579	6 months	0.749 (0.616; 0.856)	0.768 (0.622; 0.883)
	1 year	0.712 (0.601; 0.812)	0.717 (0.597; 0.824)
	5 years	0.720 (0.647; 0.786)	0.719 (0.648; 0.784)
	10 years	0.675 (0.581; 0.769)	0.676 (0.585; 0.766)
2	3 months	0.761 (0.647; 0.858)	0.773 (0.647; 0.874)
N=1007	6 months	0.727 (0.637; 0.808)	0.716 (0.619; 0.799)
	1 year	0.741 (0.677; 0.802)	0.735 (0.671; 0.796)
	5 years	0.707 (0.651; 0.756)	0.715 (0.663; 0.764)
	10 years	0.762 (0.692; 0.825)	0.766 (0.701; 0.831)
3	3 months	0.678 (0.565; 0.781)	0.684 (0.562; 0.792)
N=1043	6 months	0.673 (0.580; 0.756)	0.682 (0.589; 0.765)
	1 year	0.700 (0.640; 0.757)	0.704 (0.642; 0.762)
	5 years	0.728 (0.685; 0.771)	0.726 (0.683; 0.768)
	10 years	0.700 (0.630; 0.763)	0.708 (0.634; 0.773)
4	3 months	0.693 (0.604; 0.777)	0.675 (0.584; 0.763)
N=692	6 months	0.714 (0.633; 0.788)	0.707 (0.624; 0.783)
	1 year	0.640 (0.567; 0.713)	0.635 (0.562; 0.707)
	5 years	0.597 (0.537; 0.656)	0.590 (0.531; 0.650)
	10 years	0.740 (0.633; 0.830)	0.734 (0.522; 0.823)

AUC: Area under the cumulative dynamic ROC curve. 95% C.I.= 95% Confidence interval. N= number of patients. Sensitivity analysis for age, gender, FEV1%, dyspnea (mMRC), and setting of inclusion.

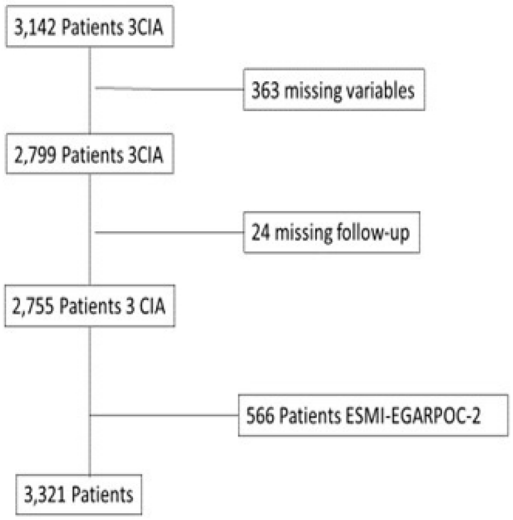
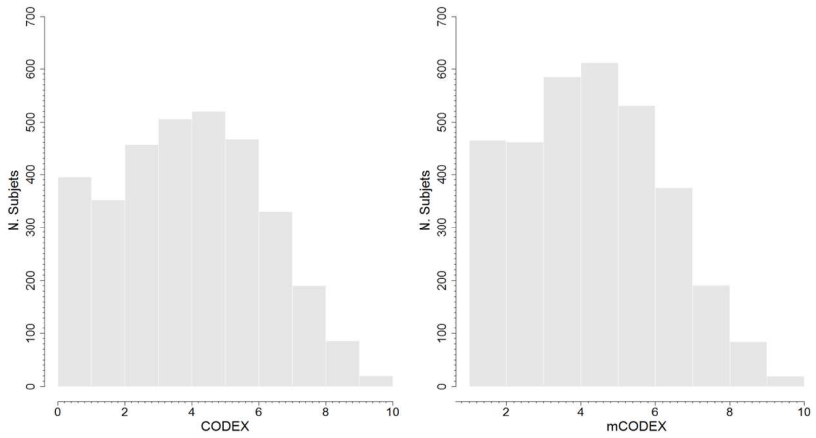
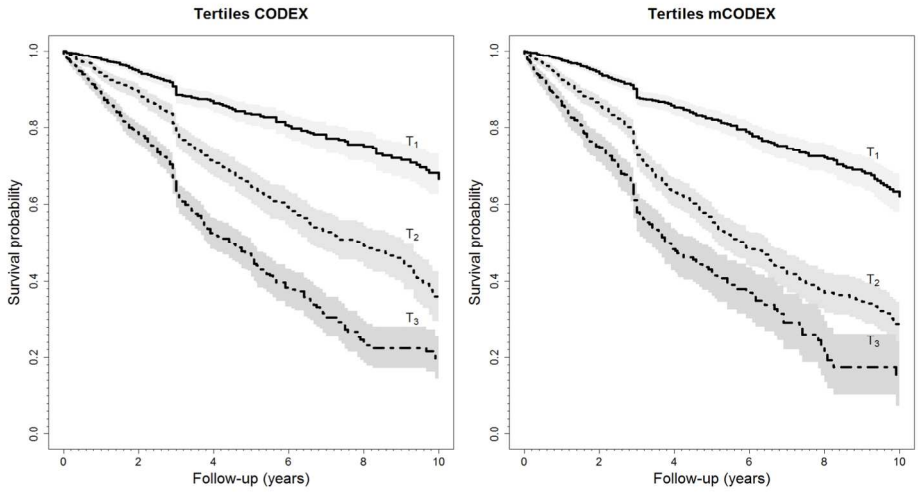


Figure 1

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) flowchart of participants and causes of exclusion.



Distribution of CODEX and mCODEX in the study population. N= number of subjects for each point of CODEX and mCODEX.



Kaplan-Meier curves for mortality stratified in tertiles for CODEX and mCODEX. The gray shading represents the 95% confidence intervals.

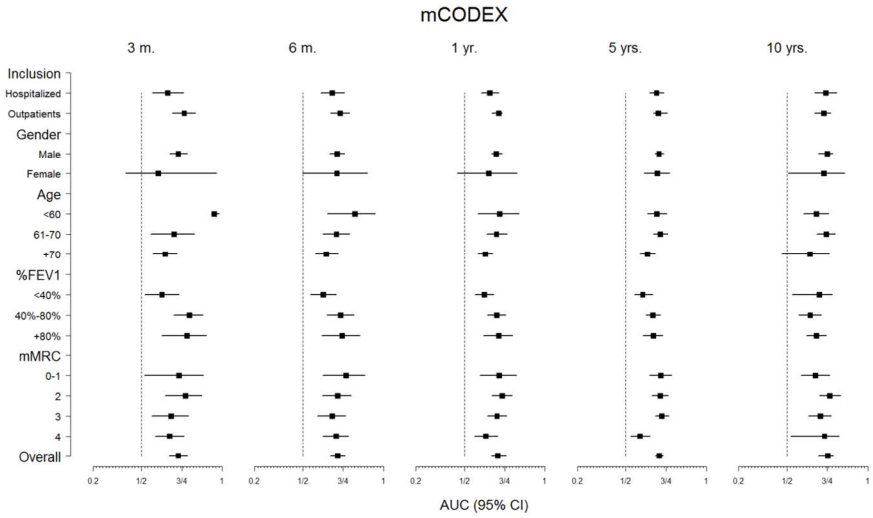


FIGURE 4B

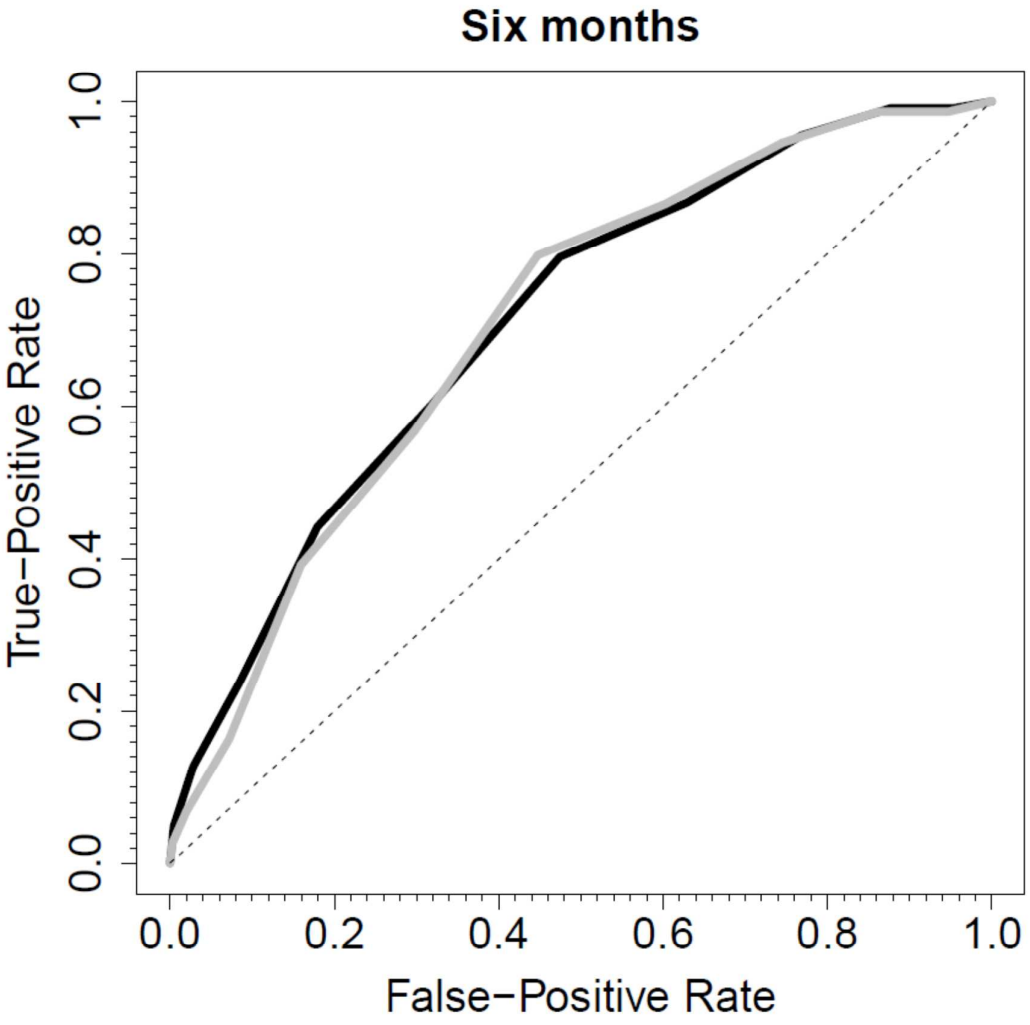
Supplementary material

Table E1.

	CODEX	m-CODEX
	Hosmer-Lemeshow test	
	p	p
3 months	0.06	0.07
12 months	0.48	021
3 years	0.83	0.79
5 years	0.48	0.7
10 years	0.53	0.76

Calibration for CODEX and mCODEX during different follow-up periods, performed with Hosmer-Lemeshow test. In this test values greater than 0.05 indicate good calibration of the model.

Figure E1 Supplementary material



Comparative/Dynamics AUCs at 6-months' mortality, ESMI (gray line), vs. total cohorts (black line)