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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

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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.

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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.

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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

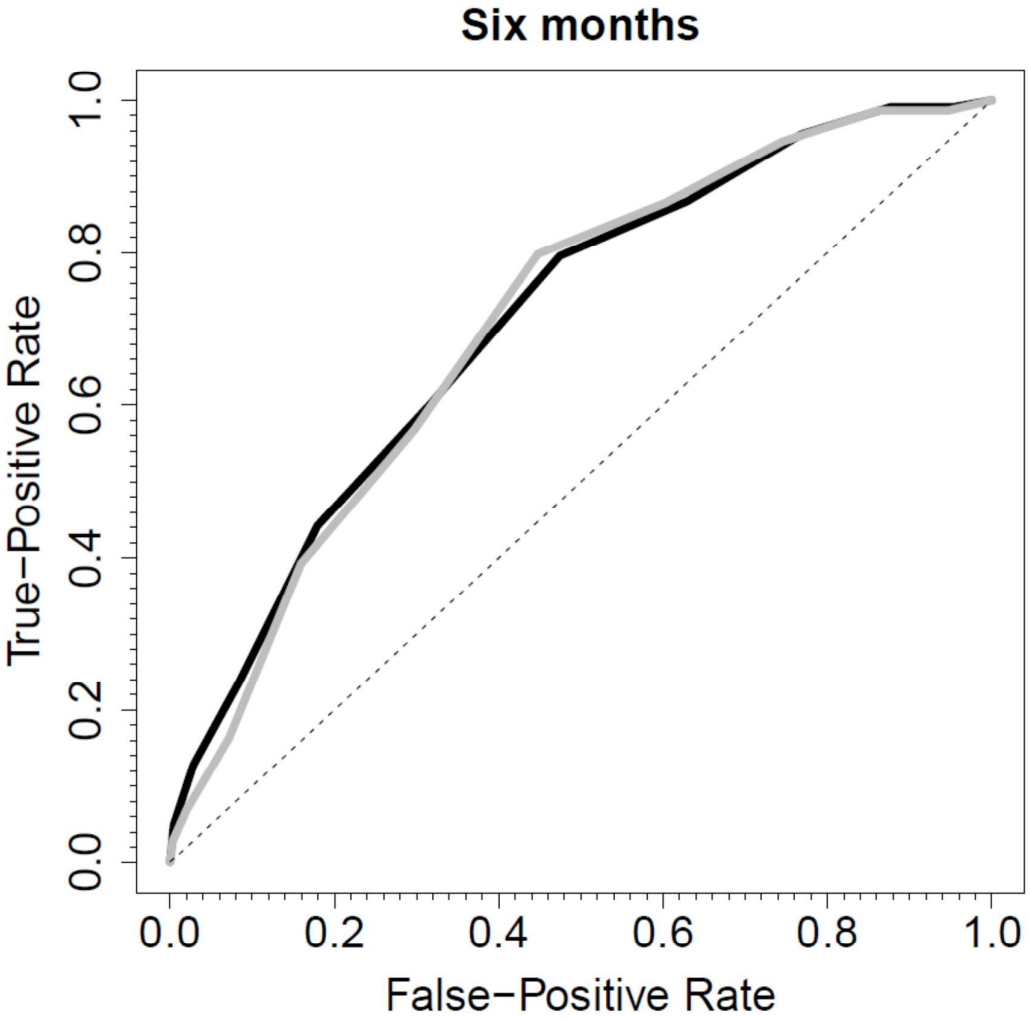
Kaplan-Meier curves for mortality stratified in tertiles for CODEX and mCODEX. The gray shading represents the 95% confidence intervals.

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.

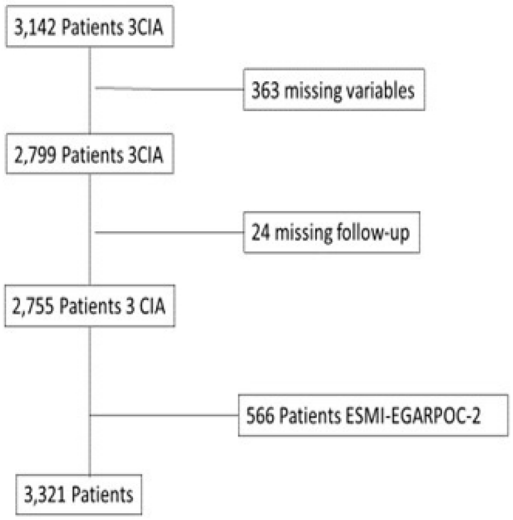
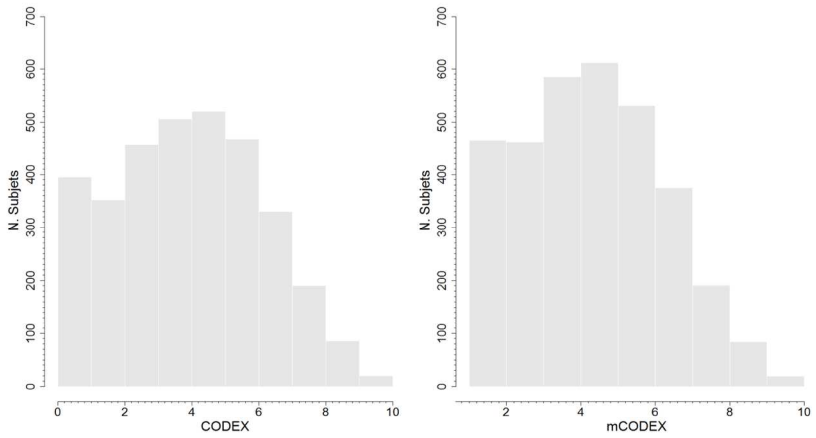
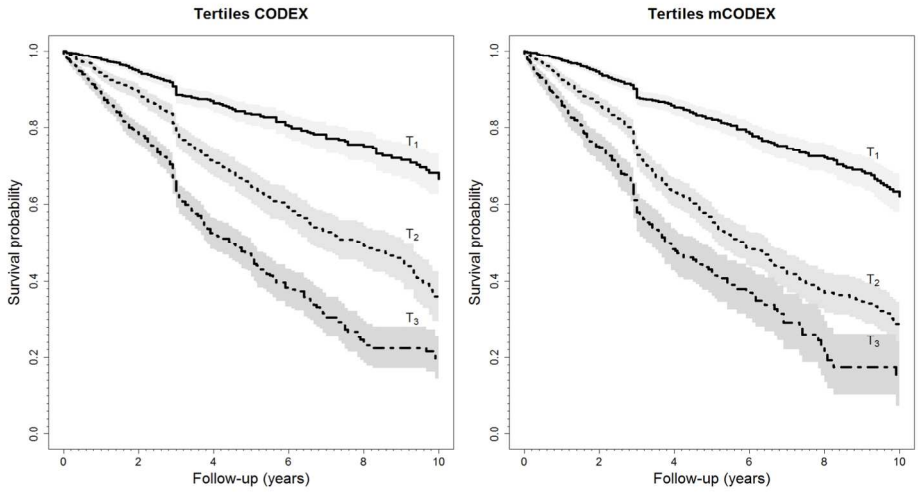


Figure 1

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.

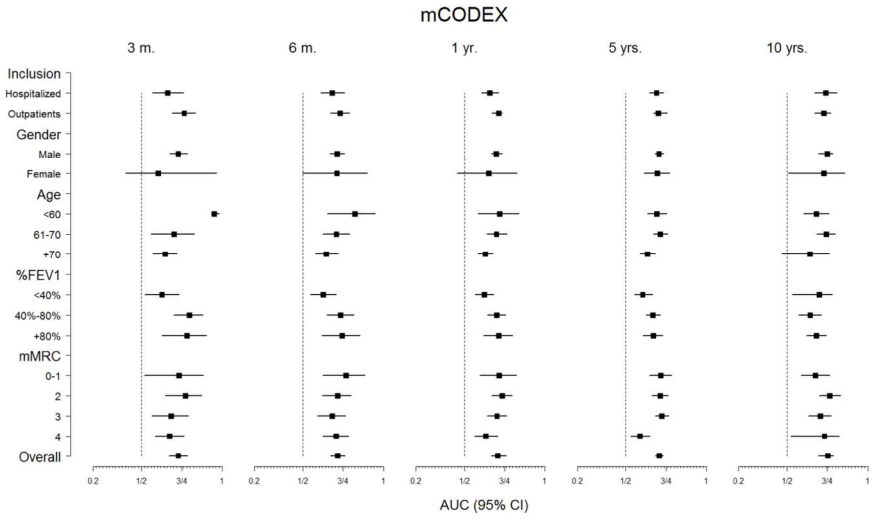


FIGURE 4B

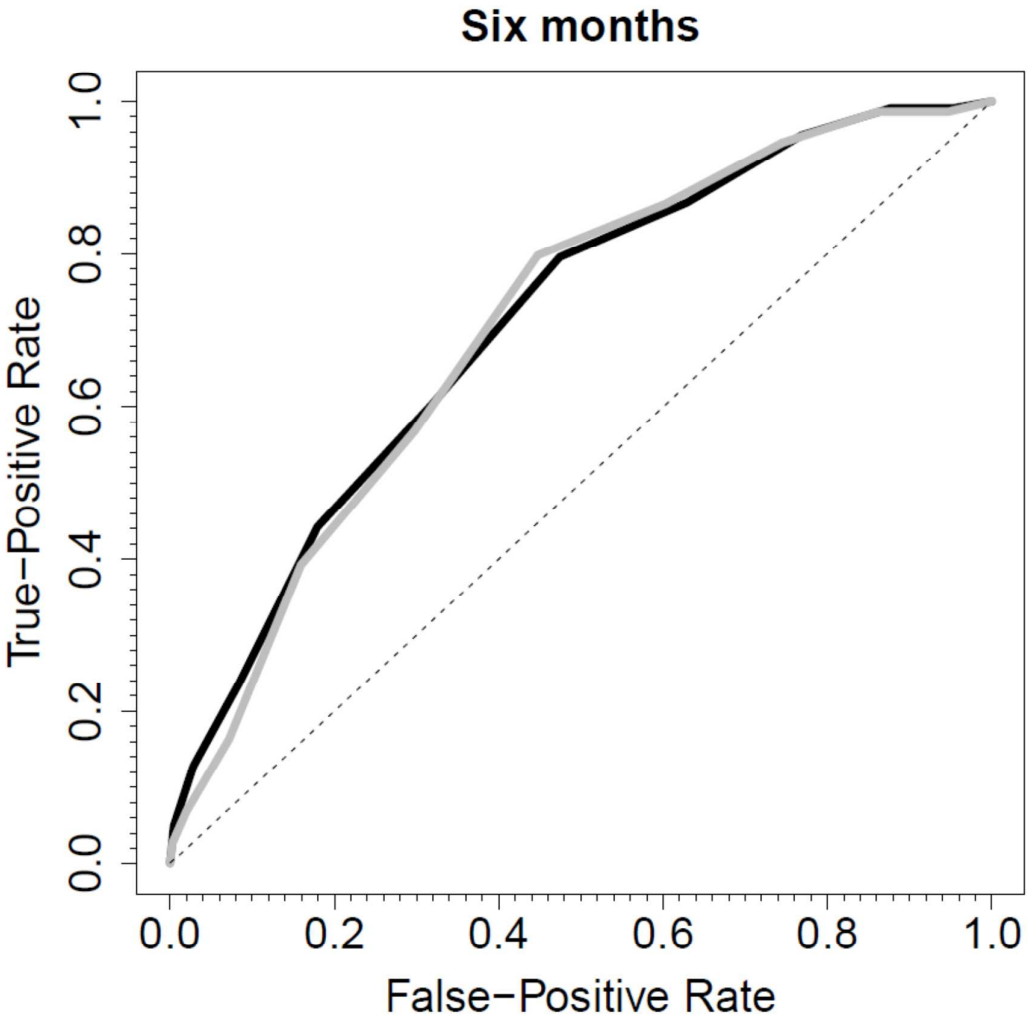
Supplementary material

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)