Recent updates of COPD exacerbation

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REVIEW

COPD Exacerbation Syndrome: The Spanish Perspective on an Old Dilemma

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Table 1 Definitions of Exacerbation According to Different Recommendation Documents

Document	Definition
GOLD 2022[74]	Acute worsening of respiratory symptoms that results in additional therapy.
GesEPOC 2021[11]	Episode of clinical instability that occurs in a patient with COPD as a result of the aggravation of the expiratory limitation to airflow or the underlying inflammatory process and is characterized by an acute worsening of respiratory symptoms with respect to the baseline situation of the individual.
Rome 2021[40]	In a patient with COPD, an exacerbation is an event characterized by dyspnea and/or cough and sputum that worsen over#14 days, which may be accompanied by tachypnea and/or tachycardia and is often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insults to the airways.

Limitation of GOLD 2022 definition

1) Highly non-specific

: confused with other diseases

(pneumonia, heart failure, acute ischemic heart disease, arrhythmia, pulmonary embolism or anxiety)

Differential diagnosis is not easy, overlapping occurs

1/5 patients with a diagnosis of exacerbation show biomarkers of ventricular dysfunction or ischemic damage

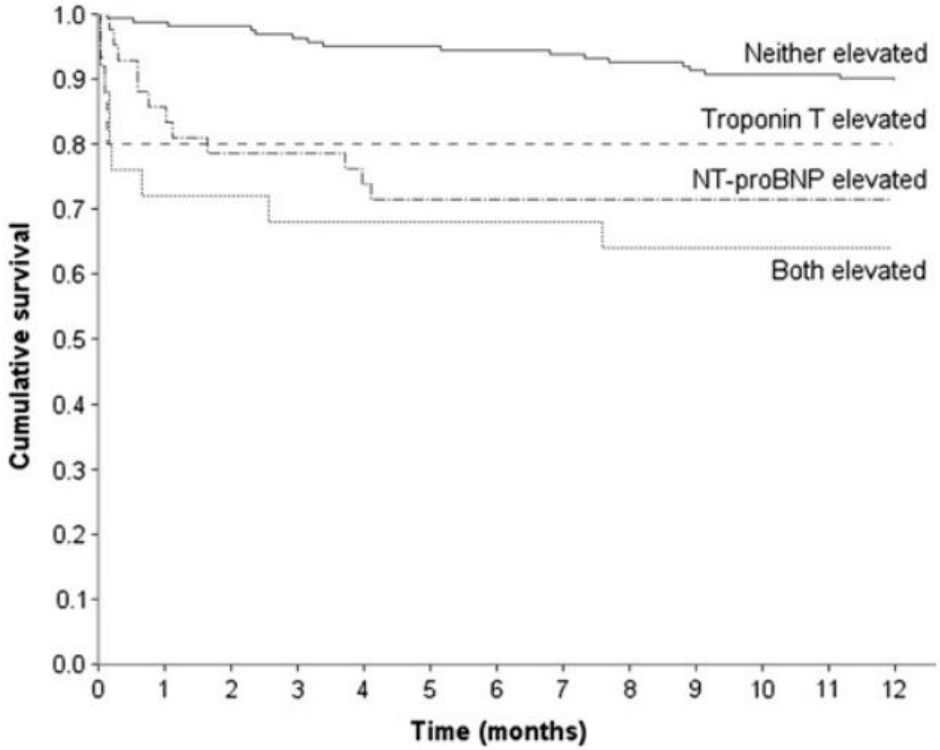

Figure 1 Kaplan—Meier survival curve for patients with acute exacerbation of chronic obstructive pulmonary disease (COPD) stratified according to cardiac biomarker status. Survival was worse in patients with both biomarkers elevated compared with patients with normal biomarkers (log-rank test, $p<0.0001$). Survivals in patients with elevated N-terminal pro-brain natriuretic protein (NT-proBNP) and cardiac troponin T alone are also significantly different from those in patients with neither biomarkers elevated (log-rank test, $p<0.001$ and $p=0.004$ respectively).

Thorax 2011; **66** i-ii Published Online First: 17 Aug 2011.

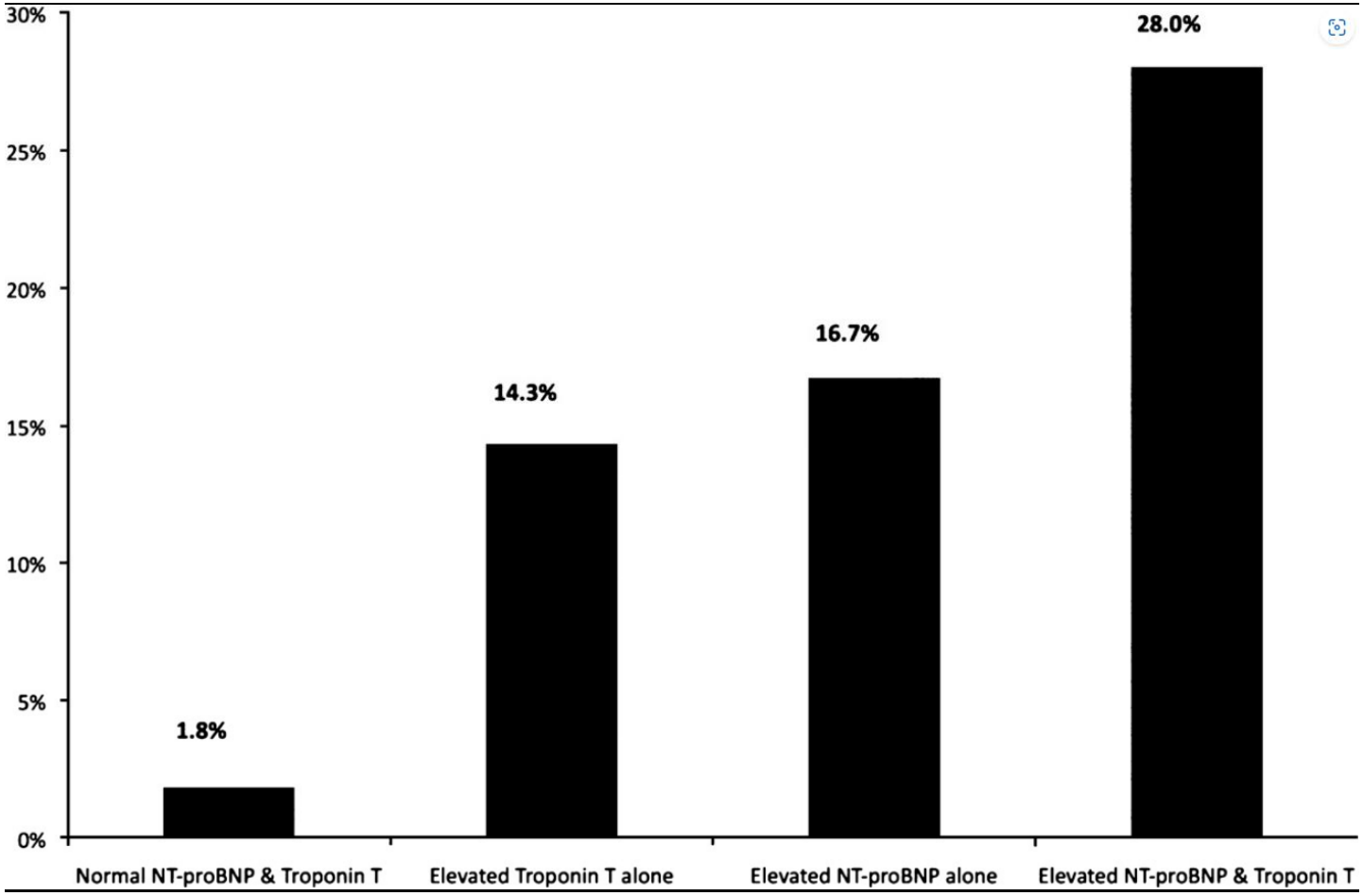

Figure 2

Thirty-day mortality after exacerbation of chronic obstructive pulmonary disease (COPD) according to markers of cardiac dysfunction status (%). Thirty-day mortality was significantly lower in patients who had normal N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin T levels (three deaths among 163 patients) compared with patients who had elevated troponin T alone (2/14, p=0.05), elevated NT-proBNP alone (7/42), p=0.0007) and both elevated troponin T and NT-proBNP (7/25, p<0.0001). Mortality between groups was compared using χ^2 test.

Thorax 2011; **66** i-ii Published Online First: 17 Aug 2011.

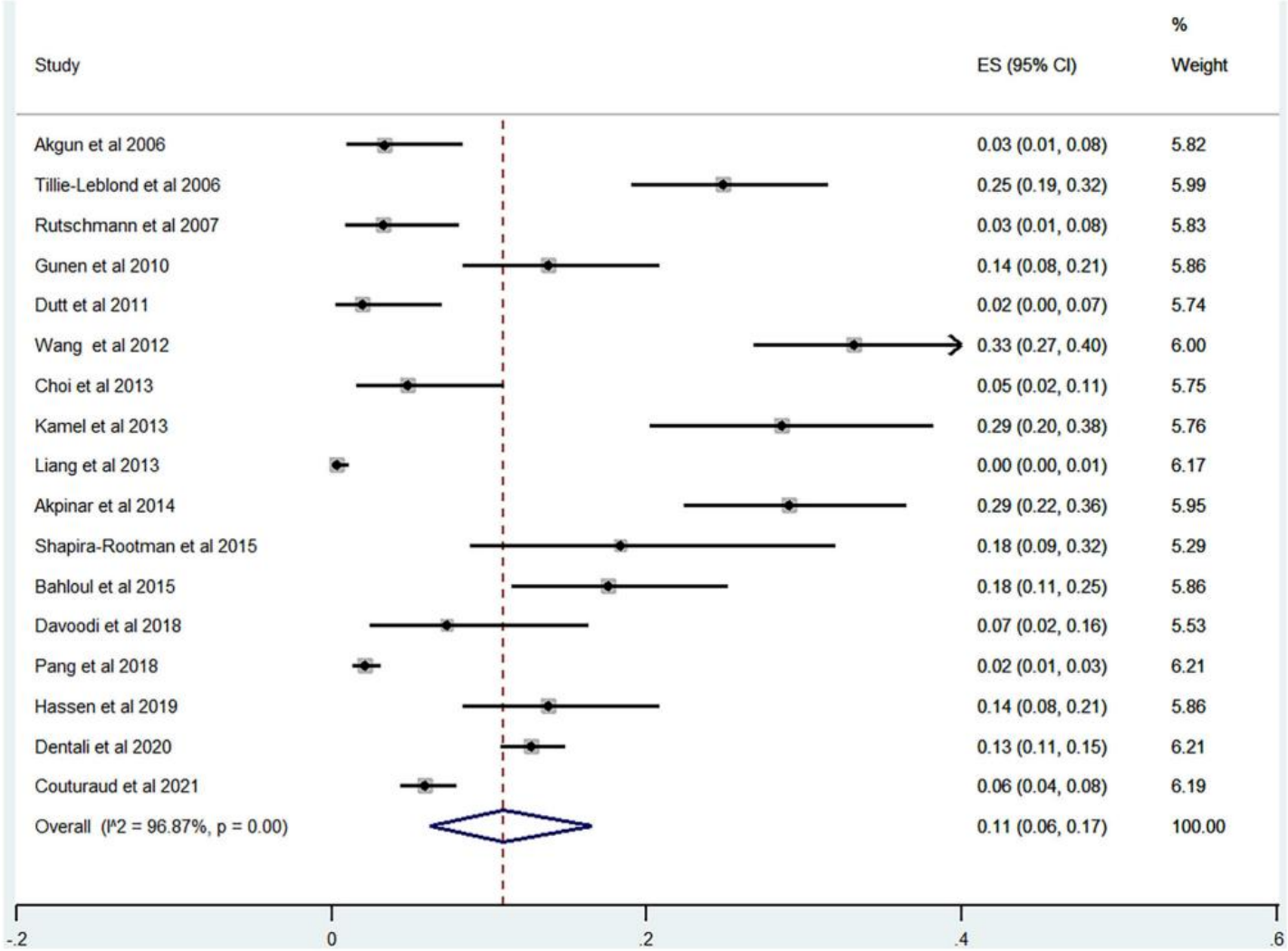

FIGURE 2 | Forest plot of prevalence of PE in AECOPD.

ORIGINAL ARTICLE | https://doi.org/10.4046/trd.2018.0087
ISSN: 1738-3536(Print)/2005-6184(Online) • Tuberc Respir Dis 2019;82:234-241

Utility of Computed Tomography in a Differential Diagnosis for the Patients with an Initial Diagnosis of Chronic Obstructive Pulmonary Disease Exacerbation

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Table 2. Changed or additional diagnosis and treatment after chest CT

Diagnosis	No. of patients	Treatment
Changed diagnosis	2/64*	Changed treatment accordingly
Pulmonary embolism	1	Anticoagulation
Lung cancer progression	1	No treatment change
Additional diagnosis	27/64	Additional examination or treatment
Pneumonia (small extents)	21†	Antibiotics in 4 patients, stop steroid in 1 patient
Lung nodule	2	PCNBx/follow up chest CT‡
Small amount pleural effusion	1	Diuretics use
Pericardial effusion	1	Follow up echocardiography
Pulmonary edema	1	Observation
Pulmonary hypertension	1	Sildenafil

*After computed tomography (CT) diagnosis was changed in two patients out of 64 patients who performed CT. †17 out of 21 patients already used antibiotics before CT was performed; to only 4 patients, antibiotics was added. ‡One patient with lung nodule performed percutaneous needle biopsy for lung nodule and squamous cell carcinoma was diagnosed but no further treatment for poor performance status. The other patient with lung nodule was examined 6 months later, and the lung nodule disappeared at follow up chest CT.

Limitation of GOLD 2022 definition

2) Underlying mechanism is not taken into account in the GOLD definition

Inflammation(pulmonary and systemic)
functional changes(worsening of airflow limitation, air trapping)
-> key symptoms

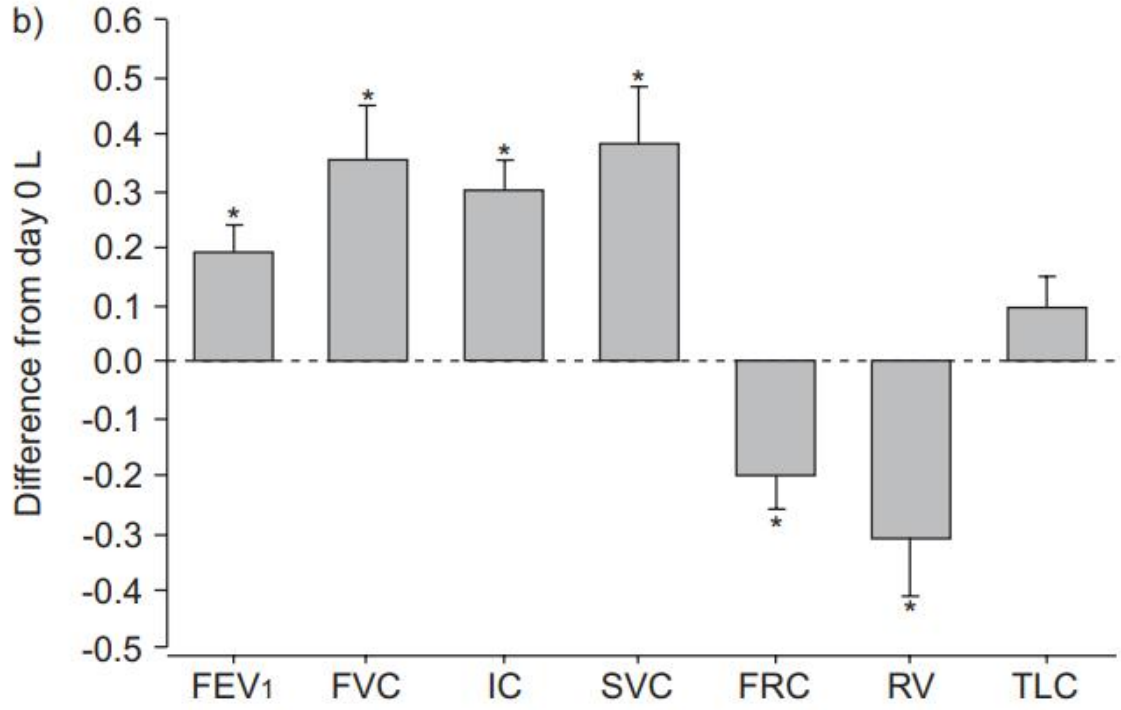


FIGURE 1. Changes in spirometric and lung volume measurements from day 0 to the final visit in all completed patients (n=20). FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; PEFR: peak expiratory flow rate; $FEF_{25-75\%}$: forced mid-expiratory flow; IC: inspiratory capacity; SVC: slow vital capacity; FRC: functional residual capacity; RV: residual volume; TLC: total lung capacity. *: $p<0.05$ difference from day 0.

Limitation of GOLD 2022 definition

3) It does not recognize the heterogeneity and complexity of the exacerbation, although different phenotypes or endotypes have been described.

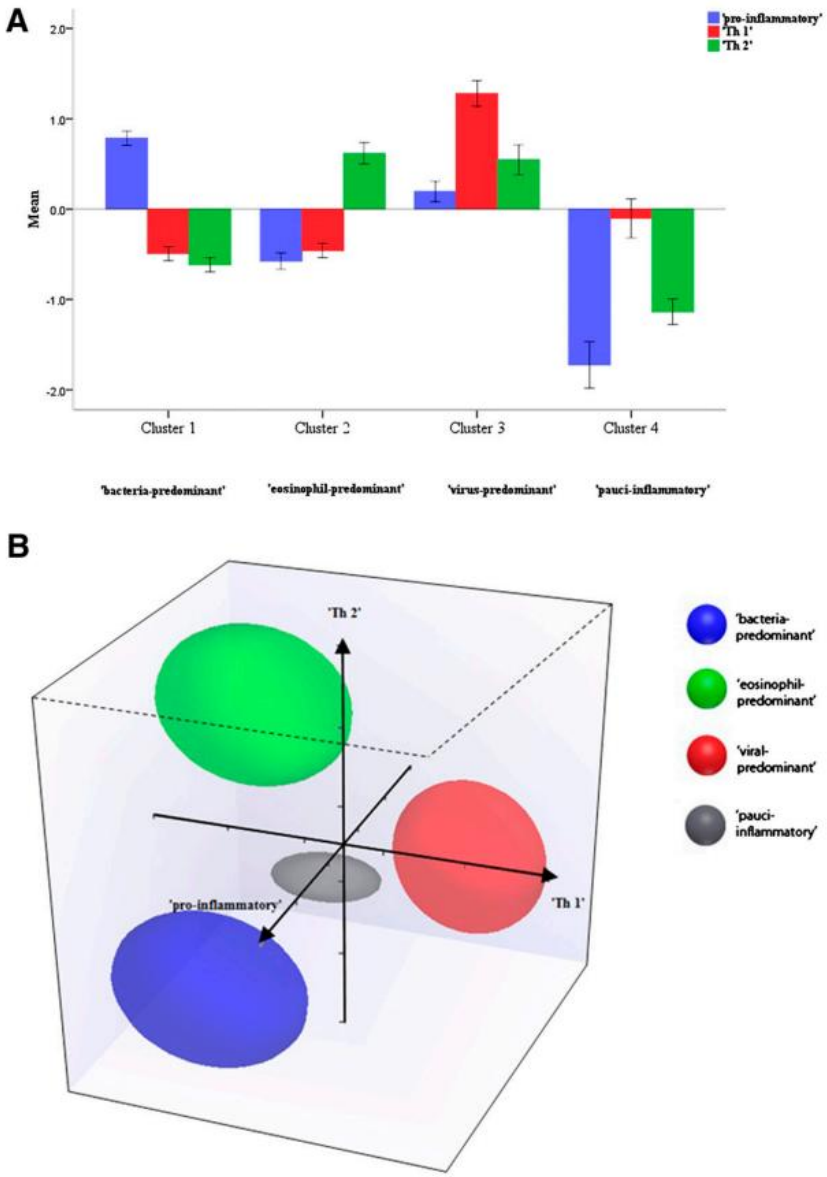
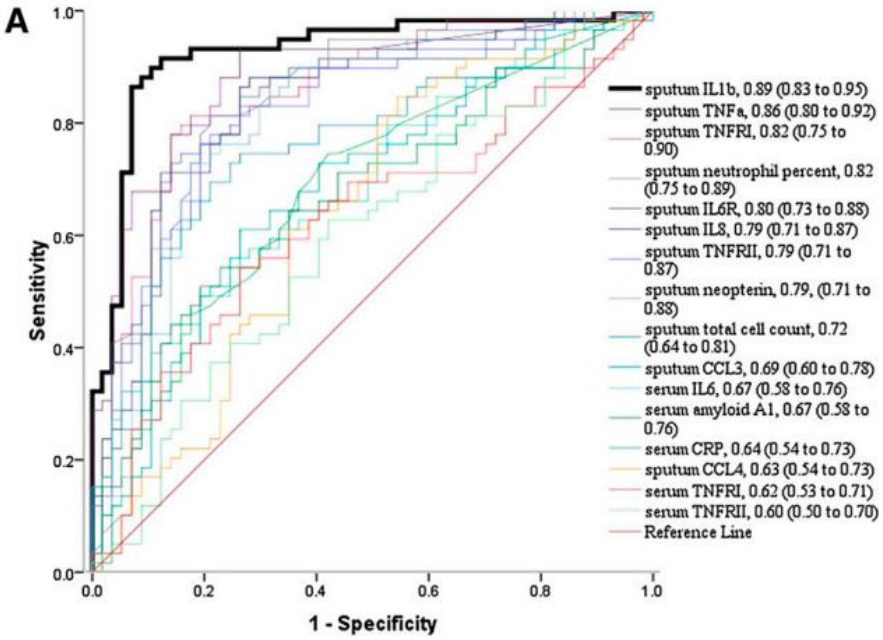


Figure 2. (*A*) Bar chart representing the mean factor scores for the three identified biologic factors (proinflammatory, Th1, and Th 2) categorized according to the four biologic clusters. (*B*) Proportional representation of biologic chronic obstructive pulmonary disease exacerbation clusters in three-dimensional ellipsoids. Cluster 1 is termed "bacteria-predominant" and is outlined in blue, cluster 2 is termed "eosinophil-predominant" and is outlined in green, cluster 3 is termed "virus-predominant" and is outlined in red, and cluster 4 is termed "pauciinflammatory" and is outlined in gray.



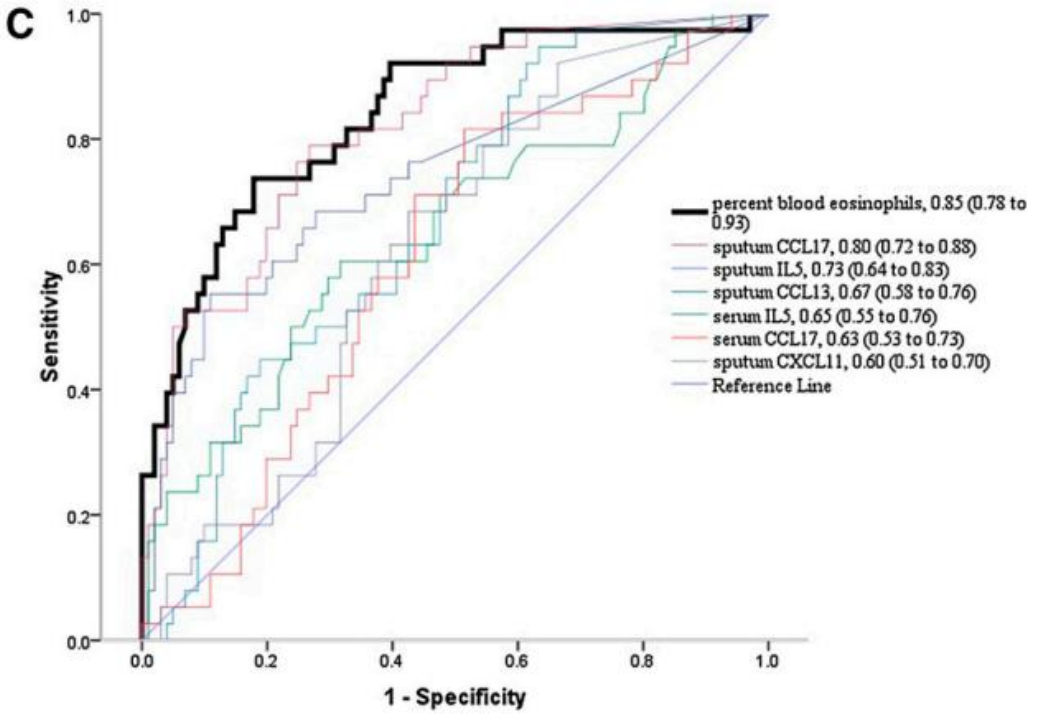


Figure 3. Receiver operating characteristic curve with area under the curve (95% confidence interval) illustrating biomarkers that positively predict (*A*) bacteria-, (*B*) virus-, and (*C*) eosinophil-associated exacerbations. Area under the curve (95% confidence interval) is shown in the parentheses. CCL = ; CRP = C-reactive protein; CXCL = ; TNF = tumor necrosis factor.

Limitation of GOLD 2022 definition

4) Although the GOLD definition includes the need for “additional treatment”, some patients suffer from worsening of respiratory symptoms at home without contact with their doctors.

TABLE 2. DESCRIPTIONS OF THE REPORTED AND UNREPORTED EXACERBATIONS

Variable	Unreported (*n* = 327)	Reported (*n* = 159)	All (*n* = 486)
Duration of symptom worsening, d			
Median (IQR)	5 (3–12)	10 (5–19)	7 (3–14)
Minimum/maximum	2/138	2/165	2/165
No. of symptoms			
Median (IQR)	2 (1–2.88)	3.42 (2.55–4.33)	2.33 (1.50–3.50)
Minimum/maximum	0.47/7	0.71/6.86	0.47/7
Type or severity of symptoms, n (%)			
Any	327 (67)	159 (33)	486
Dyspnea	236 (66)	122 (34)	358
Sputum amount	110 (54)	92 (46)	202
Sputum color	49 (47)	55 (53)	104
One symptom	119 (86)	20 (14)	139
Two symptoms	94 (75)	32 (25)	126
Three symptoms	58 (70)	25 (30)	83
Four or more symptoms	56 (41)	82 (59)	138
PEF			
Median (IQR)	186 (153–245)	182 (140–245)	185 (150–245)
Minimum/maximum	78/478	62/484	62/484
Rescue medication, per day			
Median (IQR)	1.75 (0.25–4.00)	2.38 (0.33–4.50)	2.00 (0.28–4.10)
Minimum/maximum	0/25	0/24	0/25

Definition of abbreviations: IQR = interquartile range; PEF = peak expiratory flow.

TABLE 4. RELATIONSHIP BETWEEN EVENT CHARACTERISTICS AND REPORTING

Variable	Crude HR	95% CI	Adjusted HR	95% CI
PEF change*	0.94	0.86–1.02	1.06	0.92–1.23
Rescue medication change†	1.18	1.01–1.37	1.10	0.94–1.29
Mean no. of onset symptoms‡	1.58	1.37–1.81	1.59	1.37–1.84
Increased dyspnea	1.06	0.66–1.71	0.78	0.48–1.24
Increased sputum quantity	2.42	1.54–3.80	1.55	0.94–2.54
Sputum color	2.71	1.66–4.42	1.09	0.54–2.20
Cold symptoms	2.00	1.26–3.19	0.64	0.38–1.08
Increased cough	3.61	2.03–6.44	1.61	0.81–3.22
Increased wheeze	1.35	0.85–2.14	0.44	0.25–0.77
Sore throat	2.14	1.34–3.42	0.91	0.51–1.53
Weekend	0.33	0.21–0.53	0.35	0.22–0.56
Winter	1.20	0.64–2.25	1.12	0.58–2.16

Definition of abbreviations: CI = confidence interval; HR = hazard ratio; PEF = peak expiratory flow.

* Each 10 ml.

† Each activation.

‡ Each symptom.

Limitation of GOLD 2022 definition

5) The treatment has not changed in decades, probably because this non-specific definition has led to inconsistent research

Bronchodilators, systemic steroids, or antibiotics are prescribed to nearly all patients

The Rome definition

an event characterized by dyspnea and/or cough and sputum that has worsened within the last 14 days, which can be accompanied by tachypnea and/or tachycardia, and is often associated with increased local and systemic inflammation caused by airway infection, pollution, or other airway insults.

1) Time limit (less than 14 days)
2) Underlying pathophysiology
   (tachypnea, tachycardia as important clinical biomarkers)
3) Main triggering factors are indicated

Still several unresolved issues

1) Tachypnea, tachycardia -> non-specific symptoms

2) Pauci-inflammatory exacerbations ranging 14-40%

3) Definitions including precipitating factors
(airway infection, pollution or “other insults”)

COPD exacerbation syndrome (CES)

New definition in the GesEPOC 2021

Episode of clinical instability that occurs in a patient with COPD as a consequence of worsening airflow limitation or the underlying inflammatory process and is characterized by an acute worsening of respiratory symptoms with respect to the patient's baseline situation

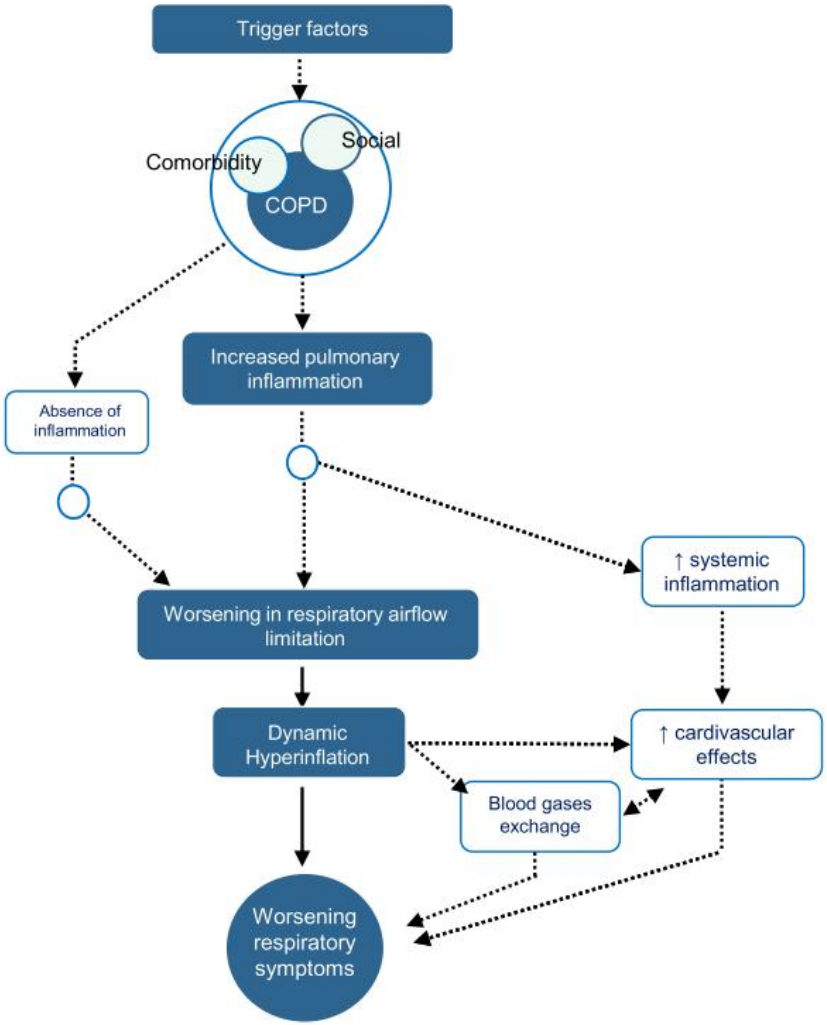


Figure 1 Pathophysiology of COPD exacerbation syndrome. Reproduced with permission from Soler-Cataluna JJ, Pinera P, Trigueros JA, et al. Spanish COPD guidelines (GesEPOC) 2021 update diagnosis and treatment of COPD exacerbation syndrome. Arch Bronconeumol. 2022;58(2):159–170.[11]

Consequences of the New Concept

Several other concomitant diseases (pneumonia, heart failure, pulmonary embolism)

-> under the umbrella of CES

the better identification and characterization of exacerbations,

by including symptoms, lung function and inflammation

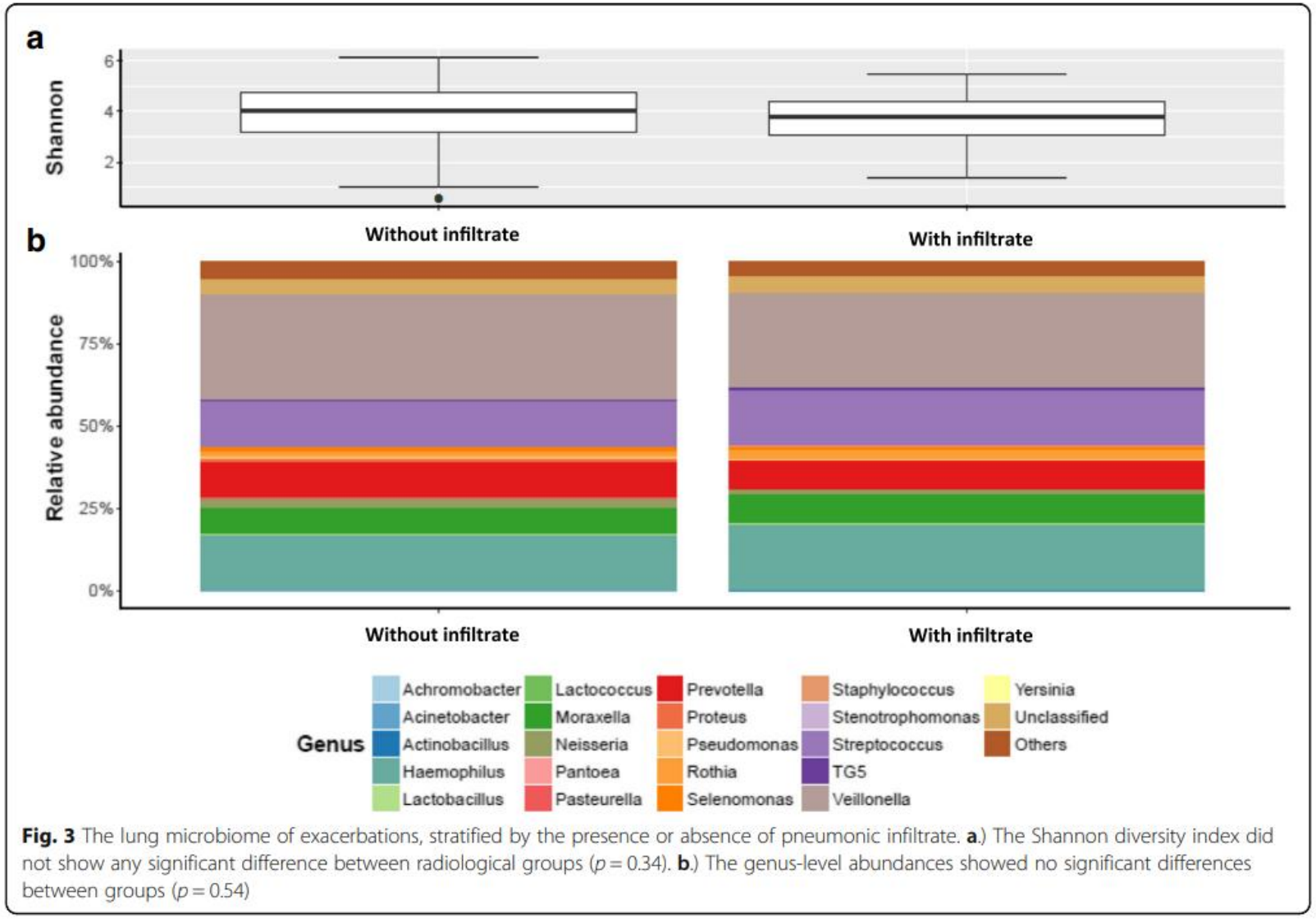


Fig. 3 The lung microbiome of exacerbations, stratified by the presence or absence of pneumonic infiltrate. **a**.) The Shannon diversity index did not show any significant difference between radiological groups ($p = 0.34$). **b**.) The genus-level abundances showed no significant differences between groups ($p = 0.54$)

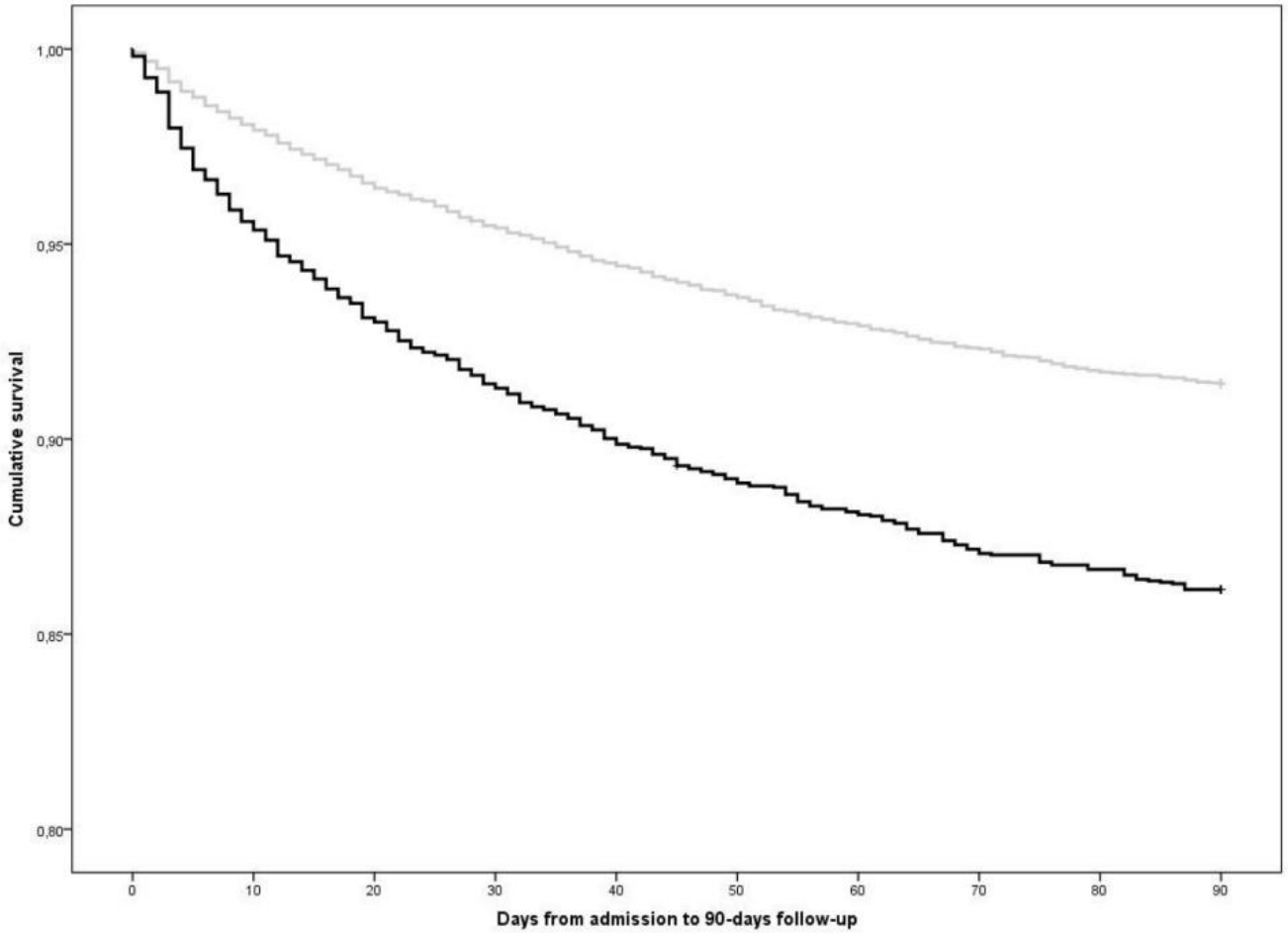


Fig 1. Kaplan-Meier curves comparing patients with and without consolidation. Black line represents patients with radiological consolidation. Grey line represents patients without consolidation.

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	Definition	In-hospital mortality
BAP-65[53]		
Class I	No risk factor and age ≤65 years	0·5%
Class II	No risk factor and age >65 years	1·4%
Class III	1 risk factor	3·7%
Class IV	2 risk factors	12·7%
Class V	3 risk factors	26·2%
DeCOPD[54]		
Mild	Score 0	0·17%
Moderate	Score 2–6	2·06%
Severe	Score 7–11	5·94%
Very severe	Score 12–18	27·91%
Roche et al, 2014[55]		
Tertile 1	Score 0	0%
Tertile 2	Score 1–2	1·6%
Tertile 3	Score 3–9	5·5%

Table: **Summary of the main severity scores for exacerbations of chronic obstructive pulmonary disease and risk of in-hospital mortality**

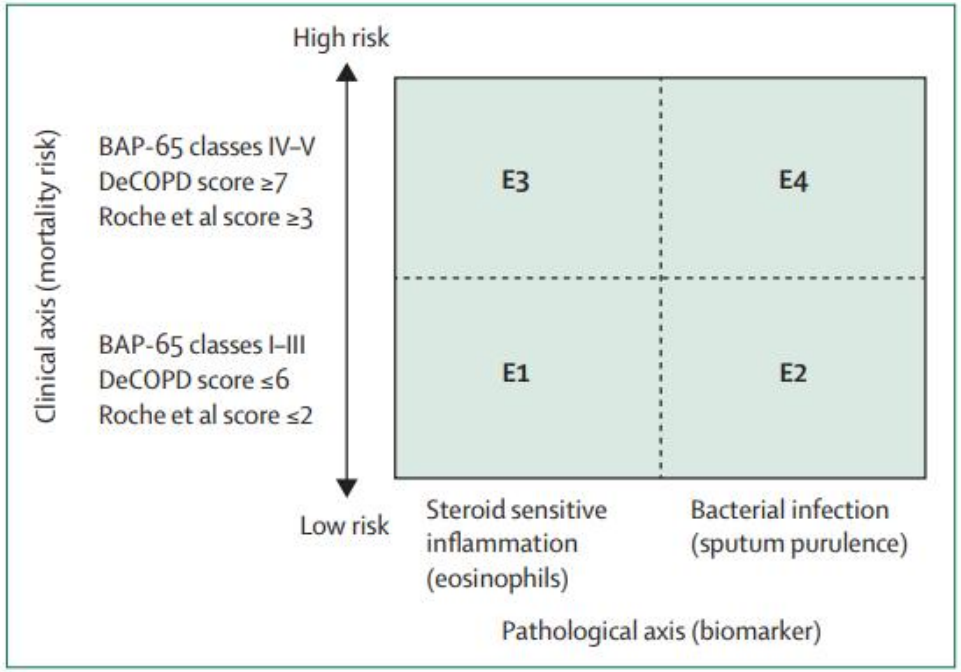

Figure: **Proposal for stratification of exacerbations of chronic obstructive pulmonary disease**
E=exacerbation.

Table 2 Treatable Trait Domains to Consider in a Patient with COPD Exacerbation Syndrome

Treatable Traits	Biomarkers	Treatments
Endotypes		
Bacterial infection	Dark sputum CRP (≥20 mg/L) Neutrophils to Lymphocyte ratio	Antibiotic
Th2 inflammation	Blood eosinophils	Systemic corticosteroids
Ventricular dysfunction	NT-pro-BNP	Diuretics Beta-blockers ARA-II ACE inhibitors
Ischemic heart disease	Troponin	Antiaggregant Beta-blockers
Lung function		
Worsening of airflow limitation	FEV_1 PEF	Bronchodilators
Acute hypoxemic respiratory failure	PaO2 < 60 mmHg	Oxygen therapy
Acute hypercapnic respiratory failure	PaCO2 > 45 mmHg	Avoid sedative drugs / Ventilatory support
Respiratory acidosis	pH<7.35	Ventilatory support
Imagen by radiography or CT		
Pneumonia Pulmonary embolism	Infection D-dimer levels CT-angiography	Antibiotics Anticoagulants
Pulmonary hypertension	Pulmonary / aortic arteries ratio	Consider oxygen

Evaluation of severity

Traditional assessment of severity

Mild -> no specific additional treatment is prescribed

Moderate -> oral steroid or antibiotics are used

Severe -> Hospitalized

This approach does not help the physician to determine the best treatment and prognosis

Table 2. Distribution of BAP-65 Class and Corresponding Mortality by Derivation and Validation Cohorts

BAP-65 Class[a]	Description	No. (%)			
		Derivation Cohort		Validation Cohort	
		Prevalence	Mortality	Prevalence	Mortality
1	0 BAP present, age ≤65 y	7710 (17.6)	21 (0.3)	7577 (17.2)	24 (0.3)
2	0 BAP present, age >65 y	15 095 (34.4)	134 (0.9)	15 029 (34.0)	146 (1.0)
3	1 BAP present	17 402 (39.7)	366 (2.1)	17 798 (40.3)	400 (2.3)
4	2 BAP present	3396 (7.7)	213 (6.3)	3478 (7.9)	225 (6.5)
5	3 BAP present	290 (0.7)	40 (13.8)	299 (0.7)	42 (14.1)

[a] "B" stands for blood urea nitrogen level higher than 25 mg/dL (to convert to millimoles per liter, multiply by 0.357); "A" stands for altered mental status defined as a Glasgow Coma Scale score lower than 14 or a designation of disoriented, stupor, or coma by a physician; "P" stands for pulse higher than 109/min; and "65" stands for older than 65 years.

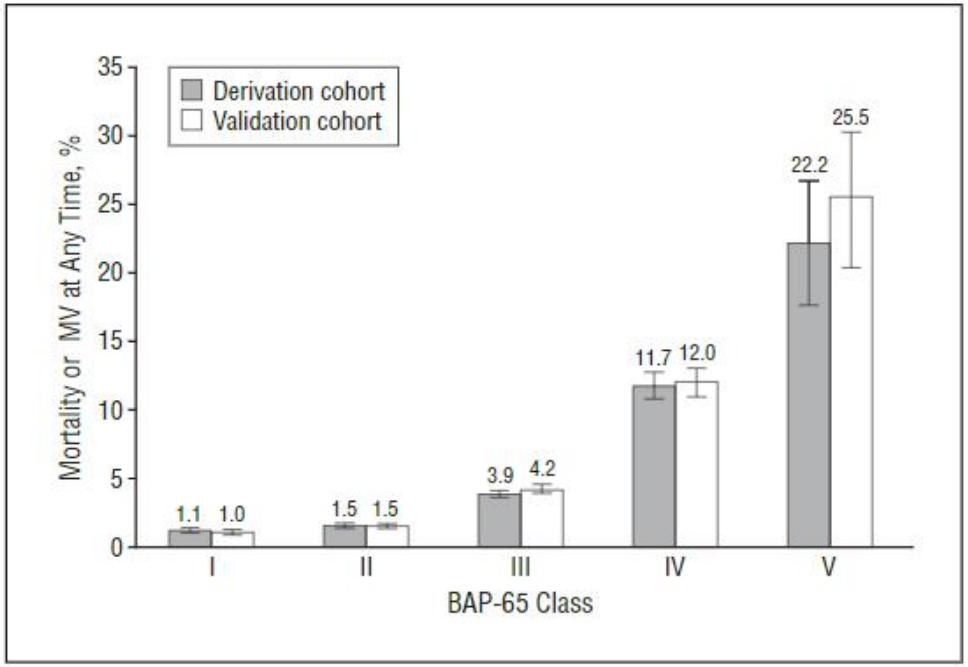

Figure 4. Mortality or mechanical ventilation (MV) at any time during hospitalization by BAP-65 class. Results are presented as median and 2.5th percentile and 97.5th percentile based on 1000 bootstrap reiterations. BAP-65 indicates blood urea nitrogen level higher than 25 mg/dL (to convert to millimoles per liter, multiply by 0.357); altered mental status, defined as a Glasgow Coma Scale score lower than 14 or a designation of disoriented, stupor, or coma by a physician; pulse higher than 109/min; and age older than 65 years.

Table 2 Independent categorical predictors of inhospital mortality

Variable	B	Odds ratio (95% CI)	Significance
eMRCD 1–4		1	
eMRCD 5a	1.63	5.11 (2.62 to 9.97)	<0.001
eMRCD 5b	1.99	7.30 (3.77 to 14.2)	<0.001
Coexistent consolidation	1.06	2.88 (1.69 to 4.90)	<0.001
Eosinophil count $<0.05 \times 10^9$/l	1.02	2.76 (1.58 to 4.83)	0.001
pH <7.3	0.99	2.68 (1.41 to 5.09)	0.003
AF	0.98	2.66 (1.39 to 5.09)	0.003
Ineffective cough	0.94	2.57 (1.37 to 4.84)	0.003
Albumin <36 g/l	0.84	2.32 (1.36 to 3.96)	0.002
Cerebrovascular disease	0.70	2.02 (1.18 to 3.42)	0.037
Age ≥80	0.70	2.01 (1.18 to 3.42)	0.011
BMI <18.5 kg/m^2	0.60	1.83 (1.00 to 3.33)	0.049
Intercept	−4.30		

AF, atrial fibrillation; BMI, body mass index; eMRCD, extended MRC dyspnoea.

Table 3 The DECAF Score

Variable	Score
Dyspnoea	
eMRCD 5a	1
eMRCD 5b	2
Eosinopenia ($<0.05 \times 10^9$/l)	1
Consolidation	1
Acidaemia (pH <7.3)	1
Atrial fibrillation	1
Total DECAF Score	6

DECAF, Dyspnoea, Eosinopenia, Consolidation, Acidaemia and atrial Fibrillation; eMRCD, extended MRC dyspnoea.

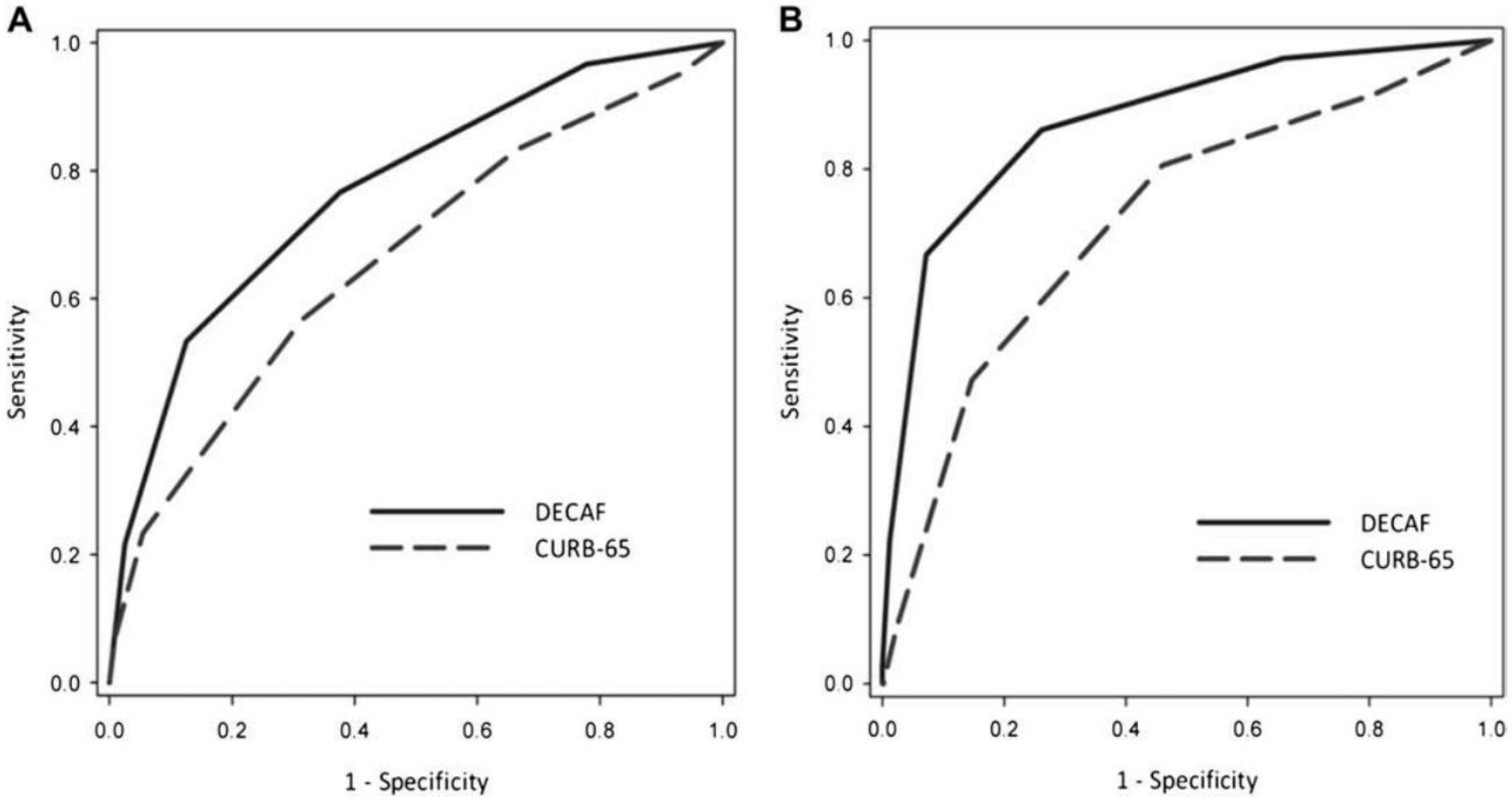

Figure 2 Receiver operator characteristic curve showing discrimination of Dyspnoea, Eosinopenia, Consolidation, Acidaemia and atrial Fibrillation (DECAF) Score and CURB-65 for inhospital mortality for patients with (n=299, panel A) and without (n=621, panel B) consolidation.

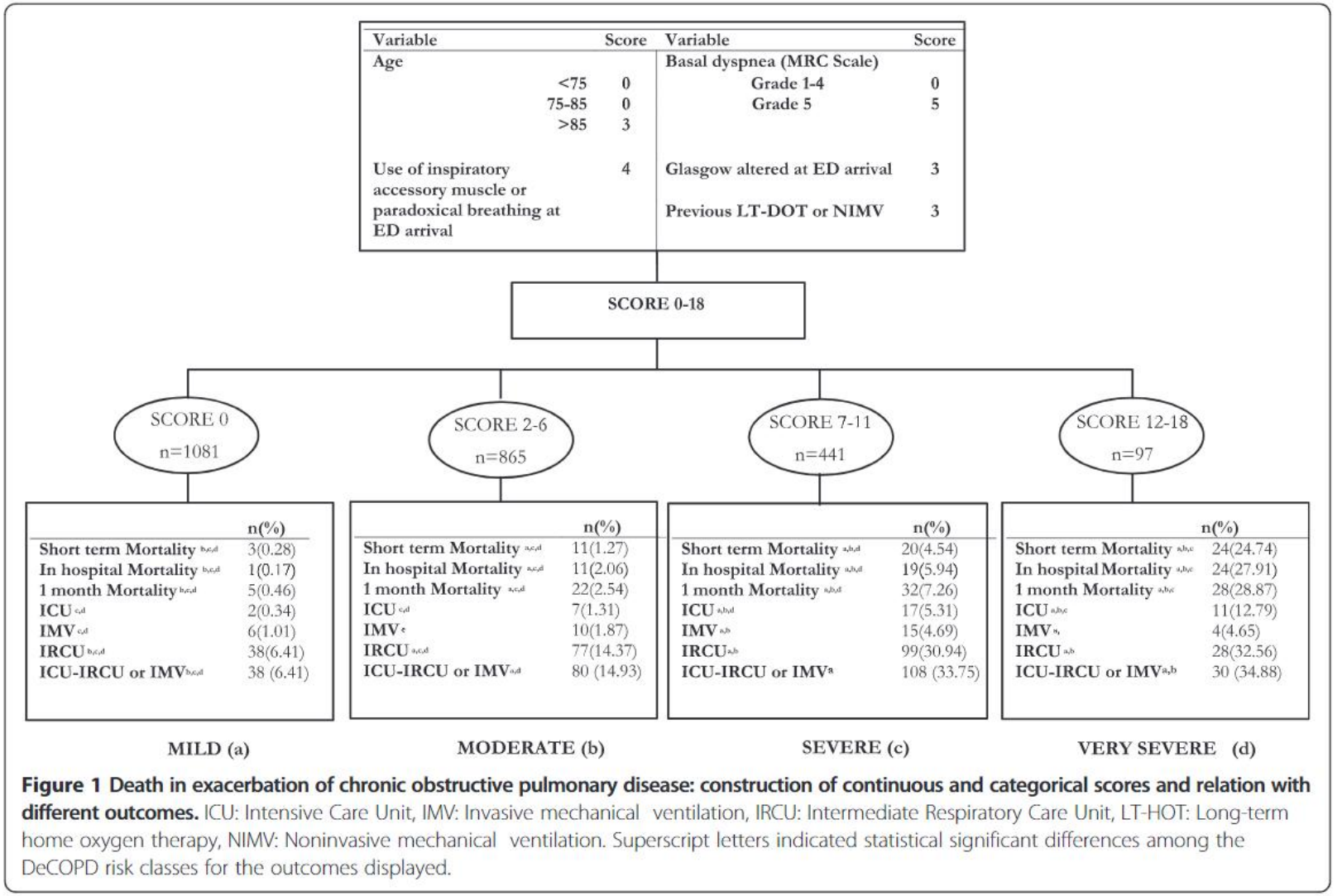

Figure 1 Death in exacerbation of chronic obstructive pulmonary disease: construction of continuous and categorical scores and relation with different outcomes. ICU: Intensive Care Unit, IMV: Invasive mechanical ventilation, IRCU: Intermediate Respiratory Care Unit, LT-HOT: Long-term home oxygen therapy, NIMV: Noninvasive mechanical ventilation. Superscript letters indicated statistical significant differences among the DeCOPD risk classes for the outcomes displayed.

Table 3 Severity Classification of COPD Exacerbation, According to GesEPOC Proposal (11)

Severity	GesEPOC Proposal Criteria for Judging Severity
Mild (All criteria must be met)	• Low-risk stratification according to baseline status* and all the following: o Dyspnea ≤ 2 (mMRC) o RR < 24 breaths/min o Resting SaO2 ≥ 95% breathing ambient air o Normal level of consciousness
Moderate (Any of the criteria must be met)	• High-risk stratification according to baseline status* and all the following: o Dyspnea ≤ 2 (mMRC) o Normal level of consciousness • Low or high-risk stratification and any of the following: o RR, 24–30 breaths/min o Resting SaO2, 90–95% breathing ambient air
Severe (Any of the criteria must be met, regardless of baseline risk level)	• Dyspnea ≥3 (mMRC) • Somnolence • RR, >30 breaths/min • Resting SaO2<90% or PaO2<60 mmHg, breathing ambient air
Very severe (Any of the criteria must be met, regardless of baseline risk level)	• Stupor / coma • pH<7.35 orPaCO2≥60 mmHg

Notes: *Baseline risk stratification according to GesEPOC (11), Low risk, Dyspnea, 0 −1 (mMRC), FEV_1>50%, 0–1 exacerbation in the last year and no hospitalizations in the last year (all criteria must be met); High risk, Dyspnea≥2 (mMRC) or FEV_1<50% or Two or more moderate exacerbations in the last year or at least 1 hospitalization in the last year.

Abbreviation: mMRC, modified Medical Research Council Dyspnea scale.

Recurrence of Exacerbations

During the clinical presentation of COPD, It is common to find patients whose exacerbations accumulate in clusters.

One exacerbation leads to future exacerbations, which increase in frequency and time proximity.

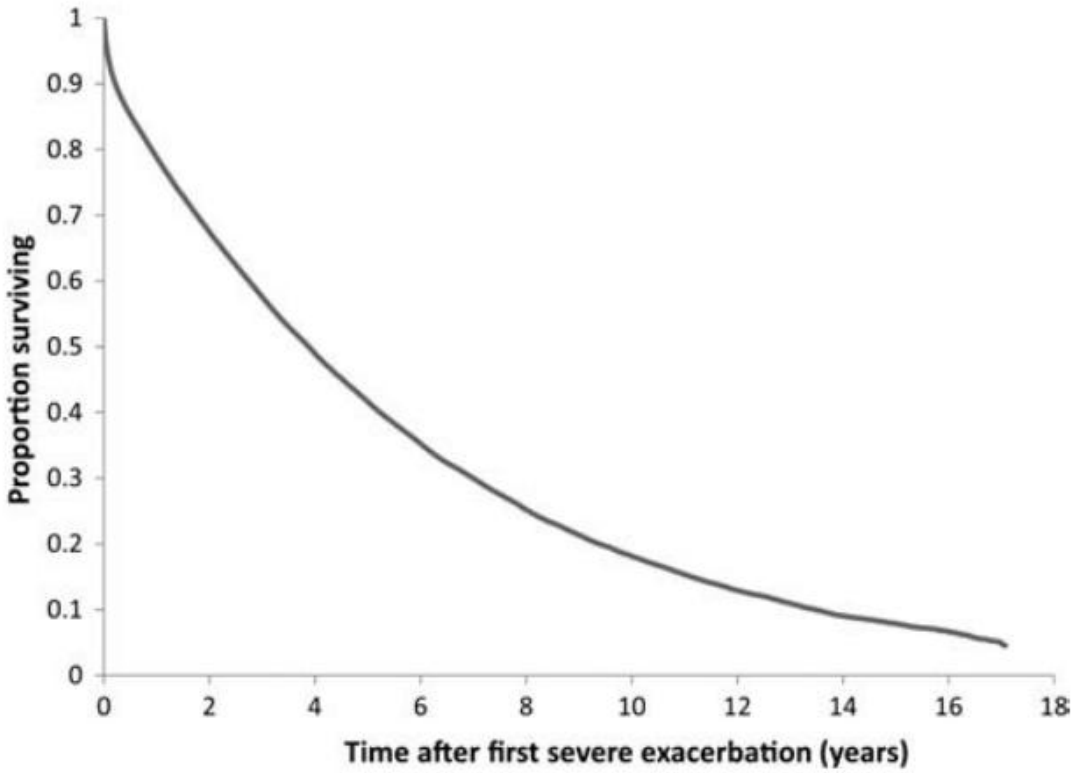

Figure 2 Kaplan–Meier survival function for the cohort of 73 106 patients from the time of their first ever hospitalisation for a chronic obstructive pulmonary disease exacerbation over the 17-year follow-up period.

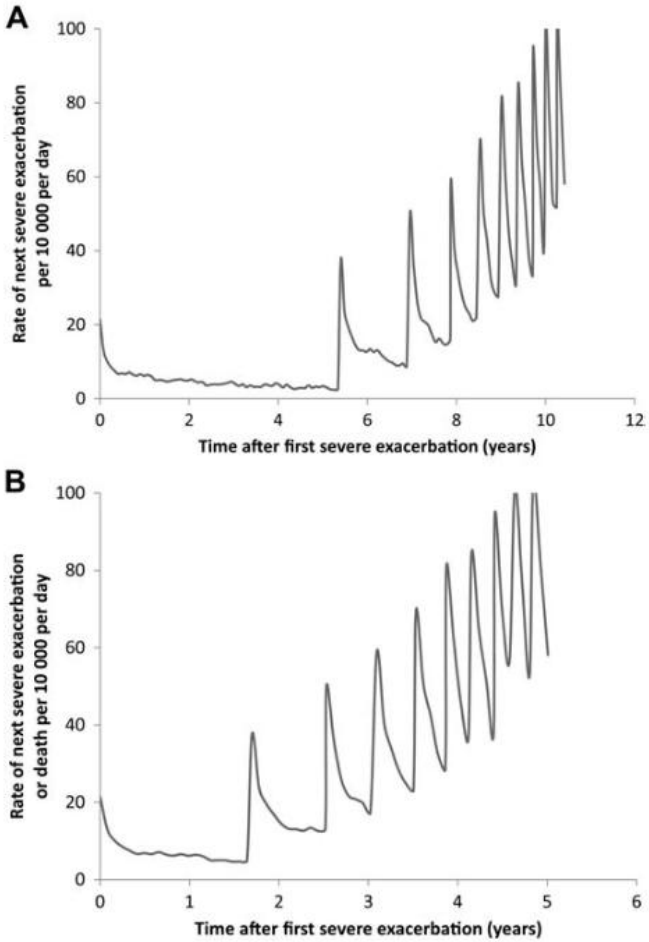

Figure 3 Hazard function of successive hospitalised chronic obstructive pulmonary disease (COPD) exacerbations (per 10 000 per day) for the cohort of 73 106 patients from the time of their first ever hospitalisation for a COPD exacerbation over the follow-up period, with the time between successive exacerbations estimated using: (A) the median inter-exacerbation times, conditional on survival with death as a competing risk; and (B) the median inter-exacerbation times as time to the next exacerbation or death, whichever occurs first.

Original Article

Impact of a Home Telehealth Program After a Hospitalized COPD Exacerbation: A Propensity Score Analysis

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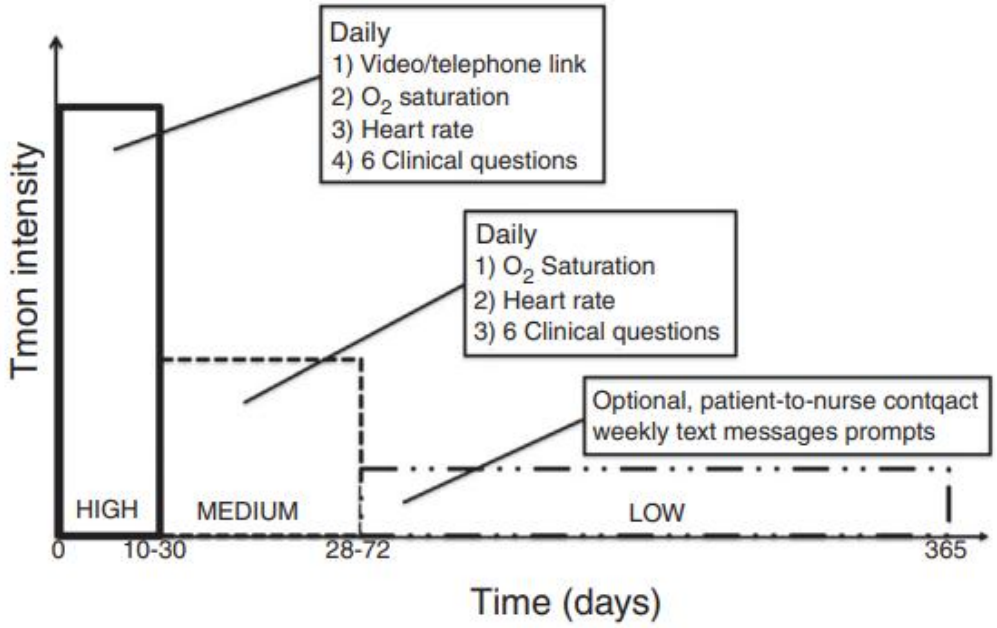


Fig. 1. Levels of intensity of telemonitoring and time of follow up. Tmon: telemonitoring, O_2: oxygen.

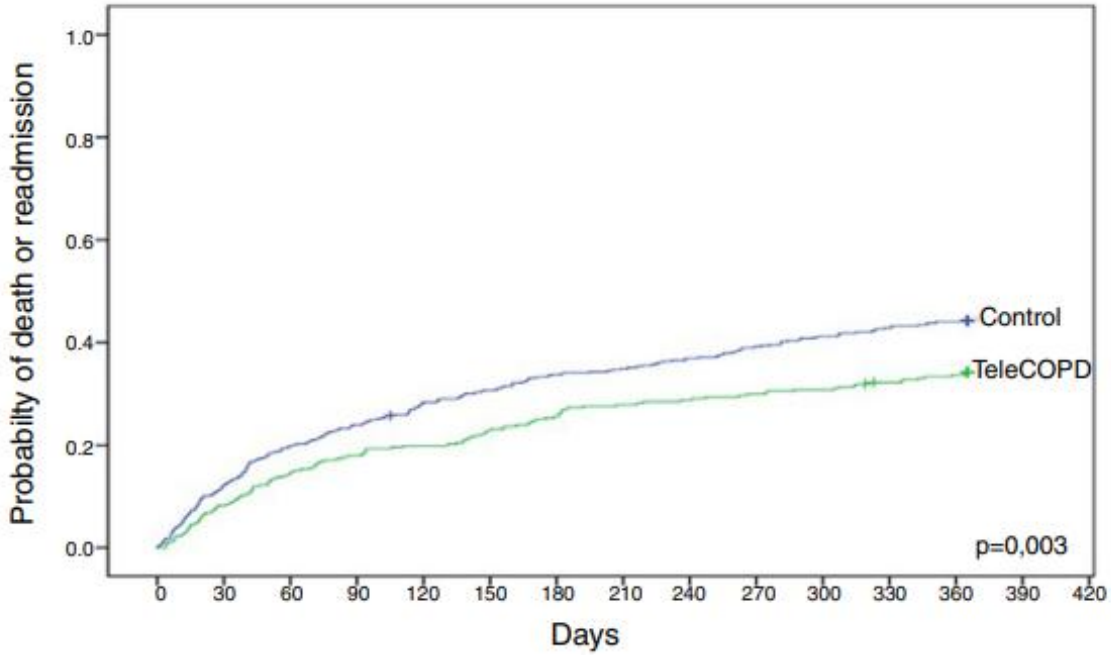
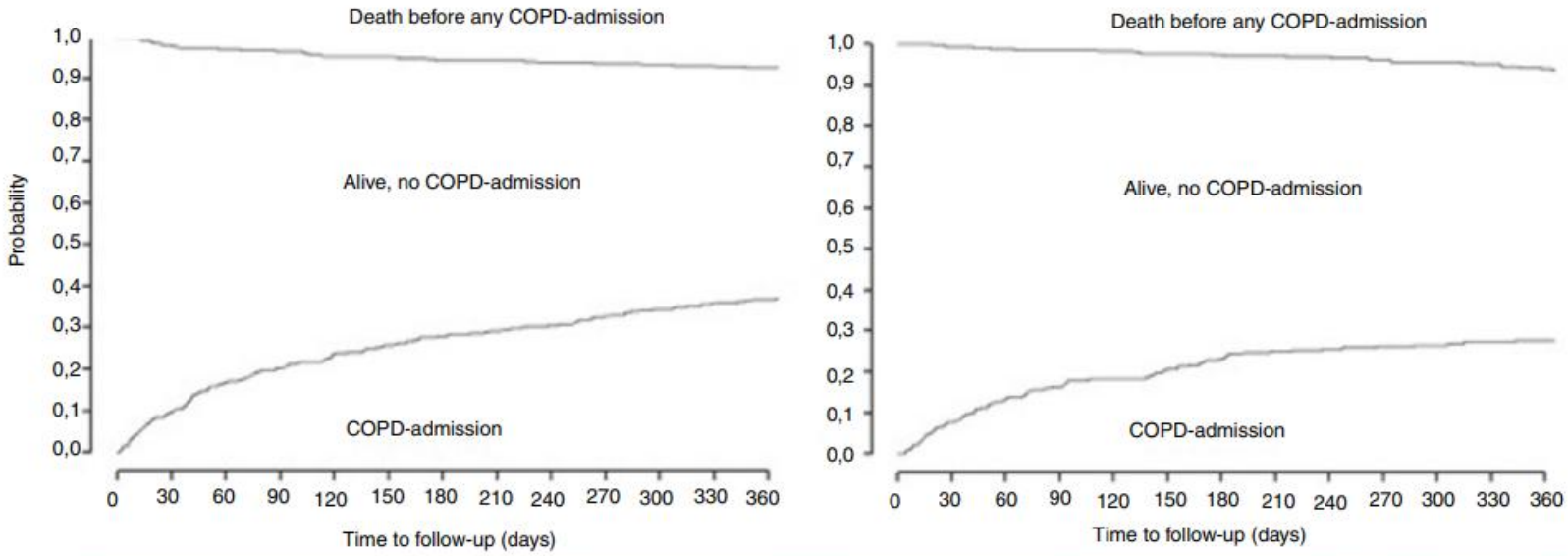


Fig. 3. Probability of death or readmission during the first year.

Control



	1 months	3 months	6 months	1 years
CONTROL				
Readmission	9.9%	20.3%	28%	36.9%
Death without readmission	2.4%	3.6%	5.7%	7.3%
Alive, without readmission	87.7%	76.1%	66.3%	55.8%
TelCOPD				
Readmission	7.7%	16.5%	23.1%	27.6%
Death without readmission	0.6%	1.4%	2.6%	6.6%
Alive, without readmission	91.7%	82.1%	74.3%	65.8%

Conclusions

Despite the advances made in recent decades, the concept of what is an exacerbation continues to be an ongoing source of debate

The GesEPOC 2021 has sought to provide an updated assessment based on the methodology of evidence-based medicine

Communication technologies applied to respiratory medicine will also help us to achieve a more personalized management of the disease