Definition, diagnosis and management of acute exacerbations of COPD: year-in-review 2024

중앙보훈병원 호흡기알레르기내과 송진화

Contents

- Definition of ECOPD
- Diagnosis of ECOPD
- Management of ECOPD
- Prevention of ECOPD

Definition of ECOPD

Definition of acute exacerbation of COPD

- Previous definition of AECOPD was “Acute worsening of respiratory symptoms that results in additional therapy”.
- GOLD 2024 adopted the Rome proposal for the definition and assessment of severity of the episodes of exacerbation of COPD at the point of care based on a number of physiological biomarkers independently of the type or site of treatment
- An exacerbation of COPD is defined as an event characterized by dyspnea and/or cough and sputum that worsen over < 14 days. Exacerbations of COPD are often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insult to the lungs.

Definition and classification of ECOPD

Rome proposal

PULMONARY PERSPECTIVE

An Updated Definition and Severity Classification of Chronic Obstructive Pulmonary Disease Exacerbations

The Rome Proposal

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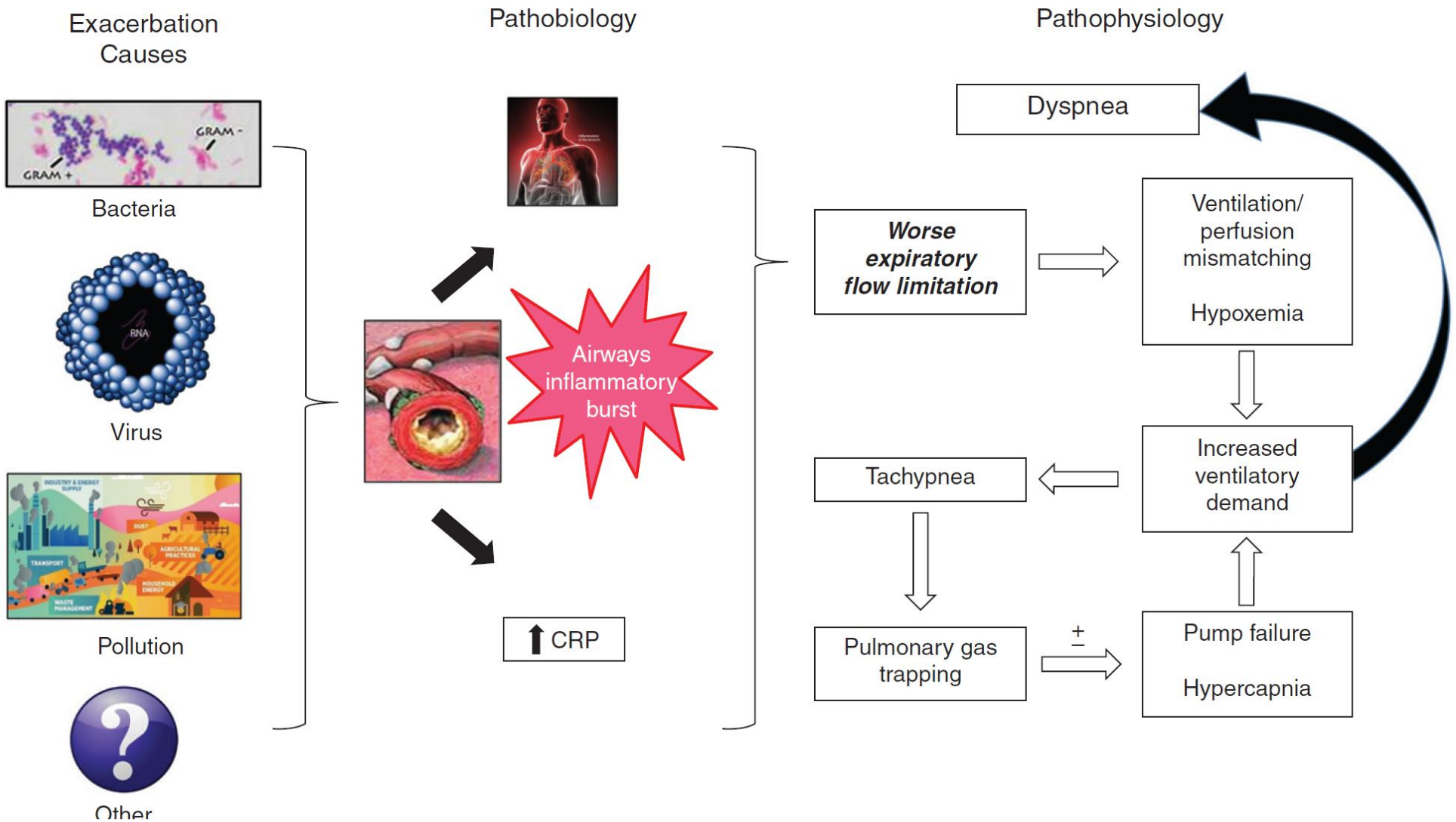
Am J Respir Crit Care Med. 2021 Dec 1;204(11):1251-1258

The Rome proposal



Am J Respir Crit Care Med. 2021 Dec 1;204(11):1251-1258

The Rome proposal

Definition	In a patient with COPD, an exacerbation is an event characterized by dyspnea and/or cough and sputum that worsen over ⩽14 d, 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 insult to the airways.
Diagnostic approach	1. These events can be life-threatening and require adequate evaluation and treatment. 2. Complete a thorough clinical assessment for evidence of COPD and potential respiratory and nonrespiratory concomitant diseases, including consideration of alternative causes for the patient's symptoms and signs: primarily pneumonia, heart failure, and pulmonary embolism. 3. Assess: a. Symptoms, severity of dyspnea as determined by using a VAS, and documentation of the presence of cough. b. Signs (tachypnea, tachycardia), sputum volume and color, and respiratory distress (accessory muscle use). 4. Evaluate severity by using appropriate additional investigations such as pulse oximetry, laboratory assessment, and CRP and/or arterial blood gases. 5. Establish the cause of the event (viral, bacterial, environmental, other).

Am J Respir Crit Care Med. 2021 Dec 1;204(11):1251-1258

The essentials of the Rome proposal

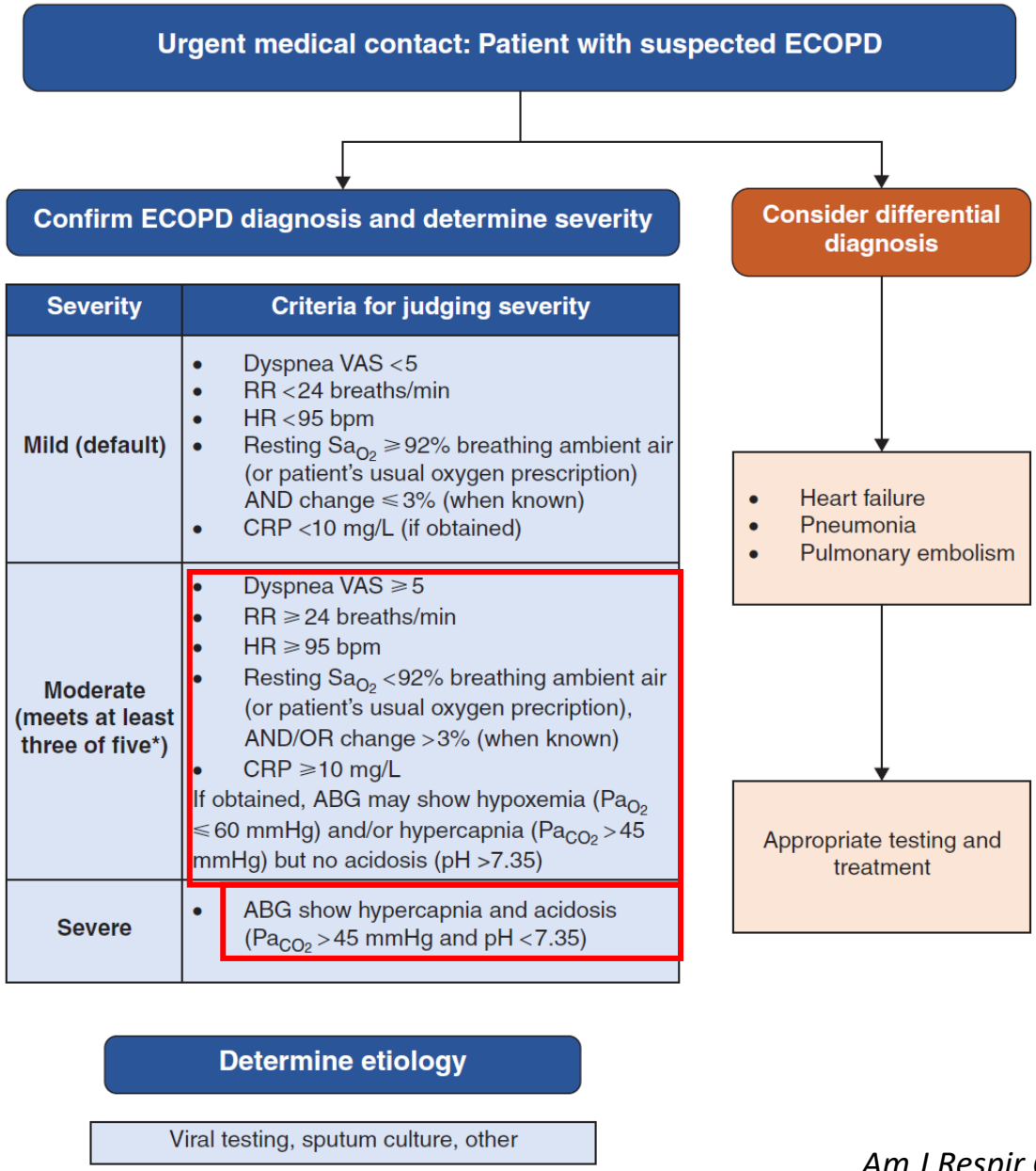
Table 1. Three definitions of COPD exacerbation

The GOLD strategy[2] COPD exacerbation is defined as the acute worsening of respiratory symptoms that results in additional therapy.
The Rome Proposal* for the definition of COPD exacerbation[1] 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 insult to the airways.
The essentials of the Rome Proposal COPD exacerbation is defined by the acute worsening associated with increased airway inflammation in a patient with COPD.

Tuberc Respir Dis (Seoul). 2022 Dec 5;86(1):61–62

Definition and classification of ECOPD

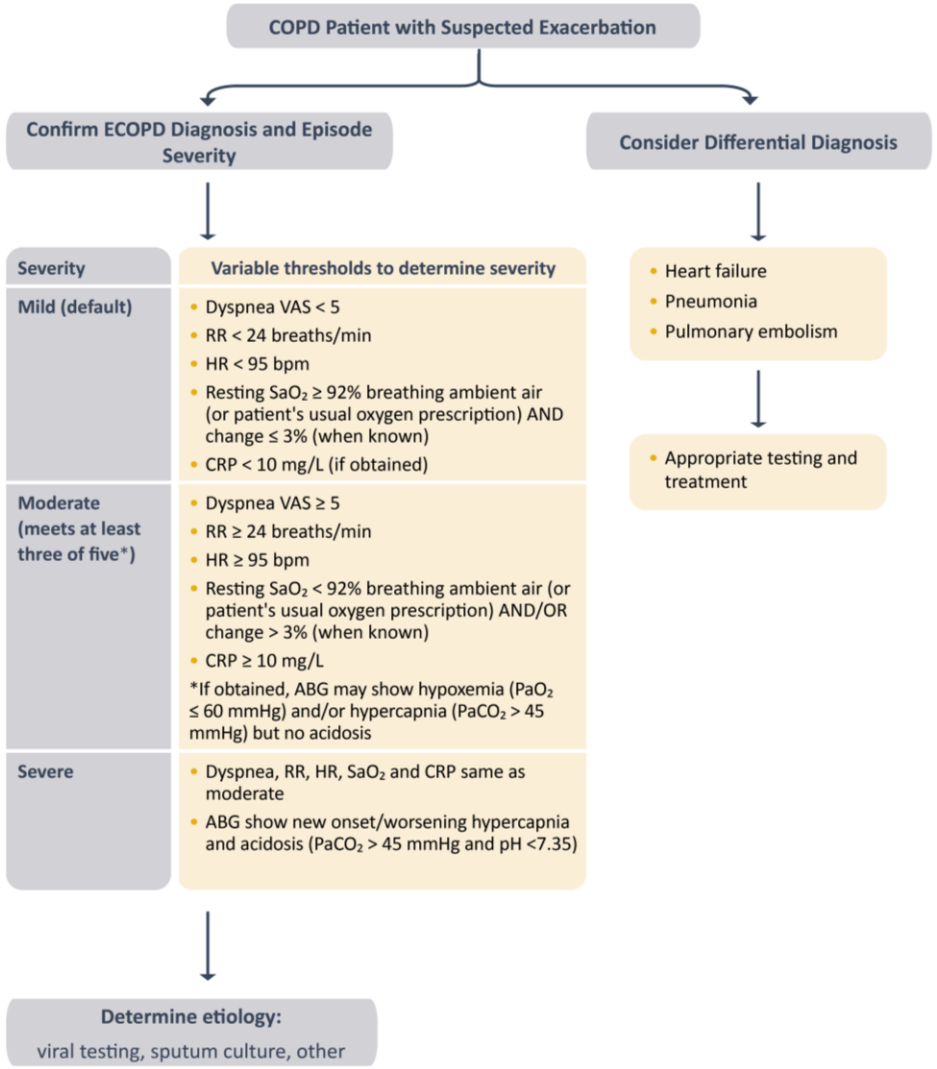
The Rome proposal



Am J Respir Crit Care Med. 2021 Dec 1;204(11):1251-1258

Classification of the Severity of COPD Exacerbations

Figure 4.3



Adapted from: The ROME Proposal, Celli et al. (2021) Am J Respir Crit Care Med. 204(11): 1251-8.

Abbreviations: VAS visual analog dyspnea scale; RR respiratory rate; HR heart rate; SaO_2 oxygen saturation; CRP C-reactive protein; ABG arterial blood gases; PaO_2 Arterial pressure of oxygen.

Rome severity classification of ECOPD

[COPD Original Research]

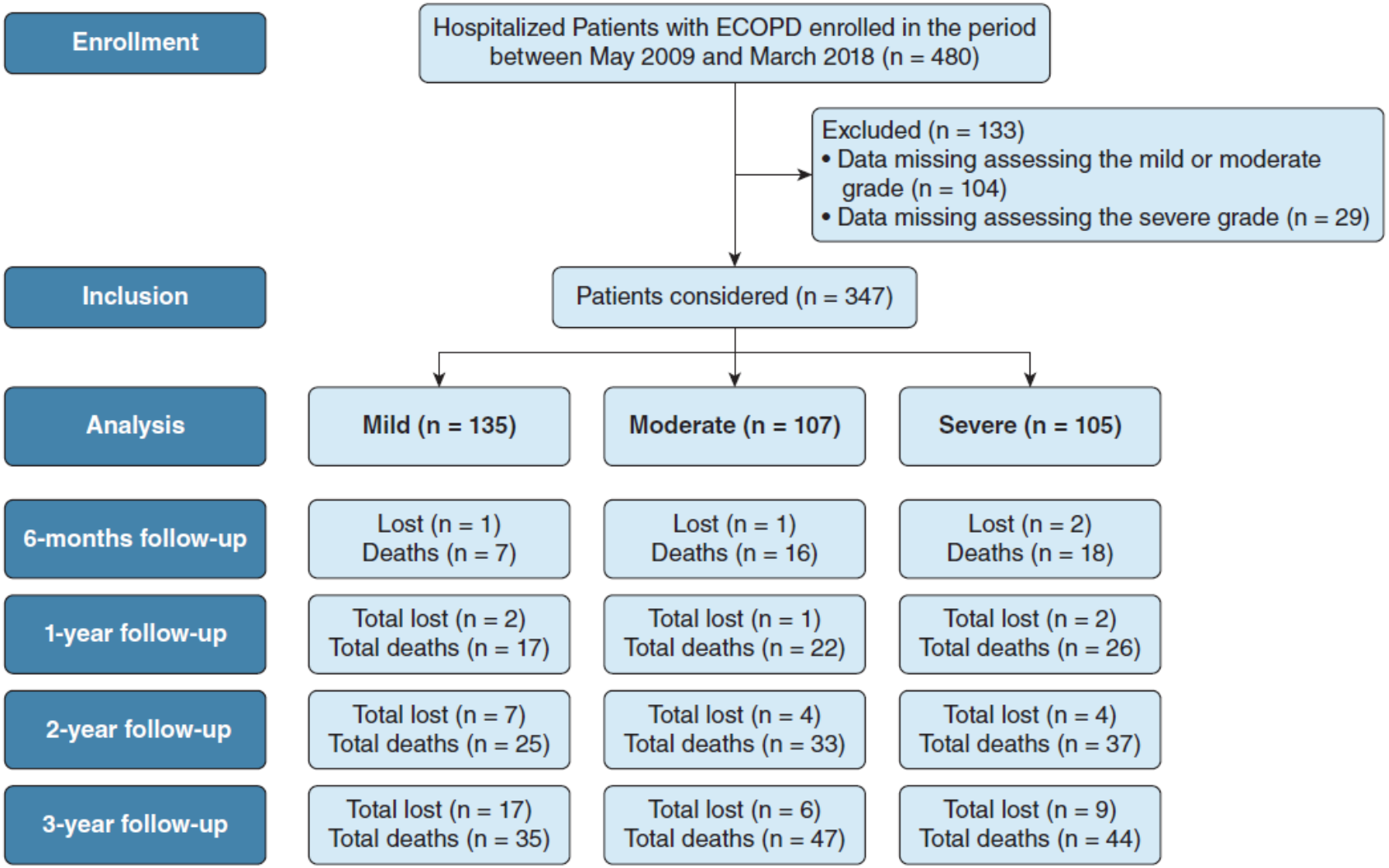
CHEST

Association Between Rome Classification Among Hospitalized Patients With COPD Exacerbations and Short-Term and Intermediate-Term Outcomes

Ernesto Crisafulli, MD, PhD; Giulia Sartori, MD; Arturo Huerta, MD, PhD; Albert Gabarrús, MSc; Alberto Fantin, MD; Néstor Soler, MD, PhD; and Antoni Torres, MD, PhD

CHEST 2023; 164(6):1422-1433

Rome severity classification of ECOPD



CHEST 2023; 164(6):1422-1433

Rome severity classification of ECOPD

TABLE 3] Study Outcomes

Variables	Mild Group (n = 135)	Moderate Group (n = 107)	Severe Group (n = 105)	*P* Value
Primary outcome				
Mortality at 1 y	17 (13)	22 (21)	26 (25)	.048[a]
Survival time, d	342 (330-355)	315 (295-335)	307 (285-328)	.032[a]
Secondary outcomes				
In-hospital mortality	4 (3)	3 (3)	4 (4)	.863
Mortality at 6 mo	7 (5)	16 (15)	18 (17)	.008[a, b]
Survival time, d	176 (171-181)	166 (158-175)	164 (155-173)	.011[a, b]
Mortality at 2 y	25 (18)	33 (31)	37 (35)	.010[a]
Survival time, d	645 (613-678)	580 (533-628)	562 (512-613)	.008[a]
Mortality at 3 y	35 (30)	47 (46)	44 (46)	.015[a, b]
Survival time, d	927 (871-982)	803 (727-878)	778 (698-857)	.004[a, b]
Length of hospital stay, d	7 [5]	7 [5]	9 [6]	.001[a, c]
NIMV	8 (6)	14 (13)	73 (70)	< .001[a, c]
IMV	2 (2)	1 (1)	12 (12)	< .001[a, c]
ICU admission	4 (3)	6 (6)	44 (43)	< .001[a, c]
New ECOPD after discharge[d]	19 (14)	19 (18)	25 (25)	.129
Readmission for ECOPD[d]	2 (1)	4 (4)	3 (3)	.579

CHEST 2023; 164(6):1422-1433

Rome severity classification of ECOPD

COPD

What Is the Association Between the Rome Severity Classification and Short- and Intermediate-Term Clinical Outcomes of ECOPD?

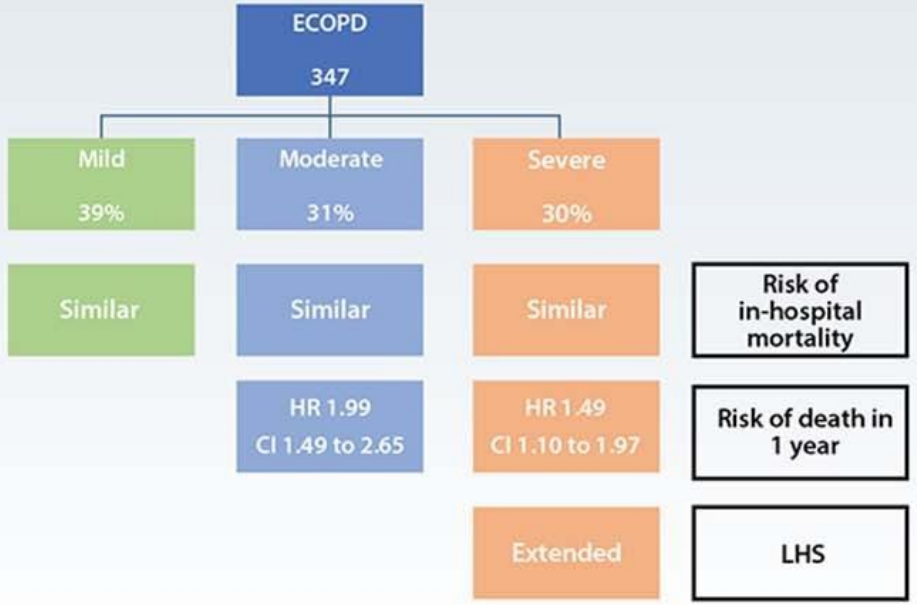
CHEST

STUDY DESIGN

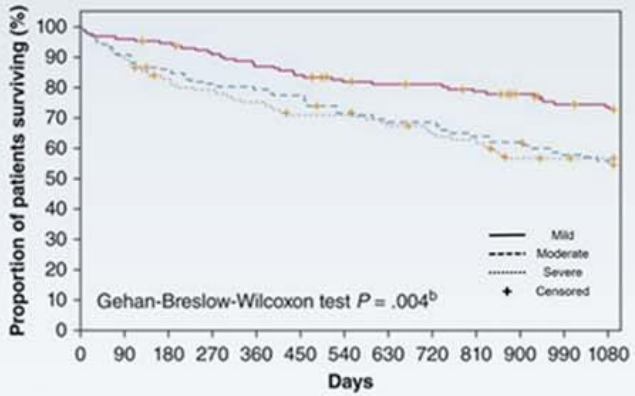
- **Retrospective analysis** of patients who are hospitalized with exacerbation of COPD (ECOPD) grouped into mild, moderate, and severe based on Rome severity classification
- Baseline, clinical, microbiologic, gas analysis, laboratory values, length of hospital stay (LHS), and mortality data were collected

RESULTS

Patient Population



Kaplan-Meier survival curves at 3 years



- *Age ≥80 years, patients requiring long-term oxygen therapy or with previous ECOPD had higher mortality*
- *A BMI between 25 kg/m² to 29 kg/m² was associated with lower risk*

The Rome classification makes it possible to discriminate patients with a worse prognosis (severe or moderate) until a 3-year follow-up.

Crisafulli E, et al. *CHEST* December 2023 | @journal_CHEST | https://doi.org/10.1016/j.chest.2023.07.021

Rome severity classification of ECOPD

ERJ OPEN RESEARCH
ORIGINAL RESEARCH ARTICLE
C. REUMKENS ET AL.

Application of the Rome severity classification of COPD exacerbations in a real-world cohort of hospitalised patients

Carmen Reumkens [1], Adrian Endres [2], Sami O. Simons [3], Paul H.M. Savelkoul [1], Roy T.M. Sprooten [4,6] and Frits M.E. Franssen [3,5,6]

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Shareable abstract (@ERSpublications)
Applying the newly proposed Rome criteria to a real-world cohort of hospitalised COPD patients provides insight into the heterogeneity of exacerbations and shows that these criteria can differentiate between events with different short-term mortality rates https://bit.ly/3l8DPep

Cite this article as: Reumkens C, Endres A, Simons SO, *et al*. Application of the Rome severity classification of COPD exacerbations in a real-world cohort of hospitalised patients. *ERJ Open Res* 2023; 9: 00569-2022 [DOI: 10.1183/23120541.00569-2022].

Rome severity classification of ECOPD

TABLE 2 Stratification of the Rome severity classification across a hospitalised COPD cohort with exacerbations of COPD (ECOPD)

	Rome classification			Traditional
	Mild	Moderate	Severe	
Patients n	52	204	108	364
Deceased in-hospital	2 (0.5)	14 (3.8)	15 (4.1)	31 (8.5)
30-day mortality	4 (1.1)	15 (4.1)	19 (5.2)	38 (10.4)
90-day mortality	4 (1.1)	28 (7.7)	27 (7.4)	59 (16.2)
Cohabiting (N=47/187/98)	26 (7.1)	117 (32.1)	53 (14.6)	196 (53.8)
Supported living (N=49/196/104)	24 (6.6)	98 (26.9)	63 (17.3)	185 (50.8)

Data are presented as n (%). Percentage is calculated out of total number of patients (N=364).

Rome classification showed difference in in-hospital mortality

ERJ Open Res 2023; 9: 00569-2022

Definition and classification of ECOPD

Rome severity classification of ECOPD

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Open Access Full Text Article ORIGINAL RESEARCH

Validation of the Rome Severity Classification of Chronic Obstructive Pulmonary Disease Exacerbation: A Multicenter Cohort Study

Jiaxin Zeng[1,*], Chen Zhou[2,*], Qun Yi[1,3], Yuanming Luo[4], Hailong Wei[5], Huiqing Ge[6], Huiguo Liu[7], Jianchu Zhang[8], Xianhua Li[9], Pinhua Pan[10], Mengqiu Yi[11], Lina Cheng[11], Liang Liu[12], Jiarui Zhang[1], Lige Peng[1], Jiaqi Pu[1], Haixia Zhou[1] On behalf of the MAGNET AECOPD Registry Investigators

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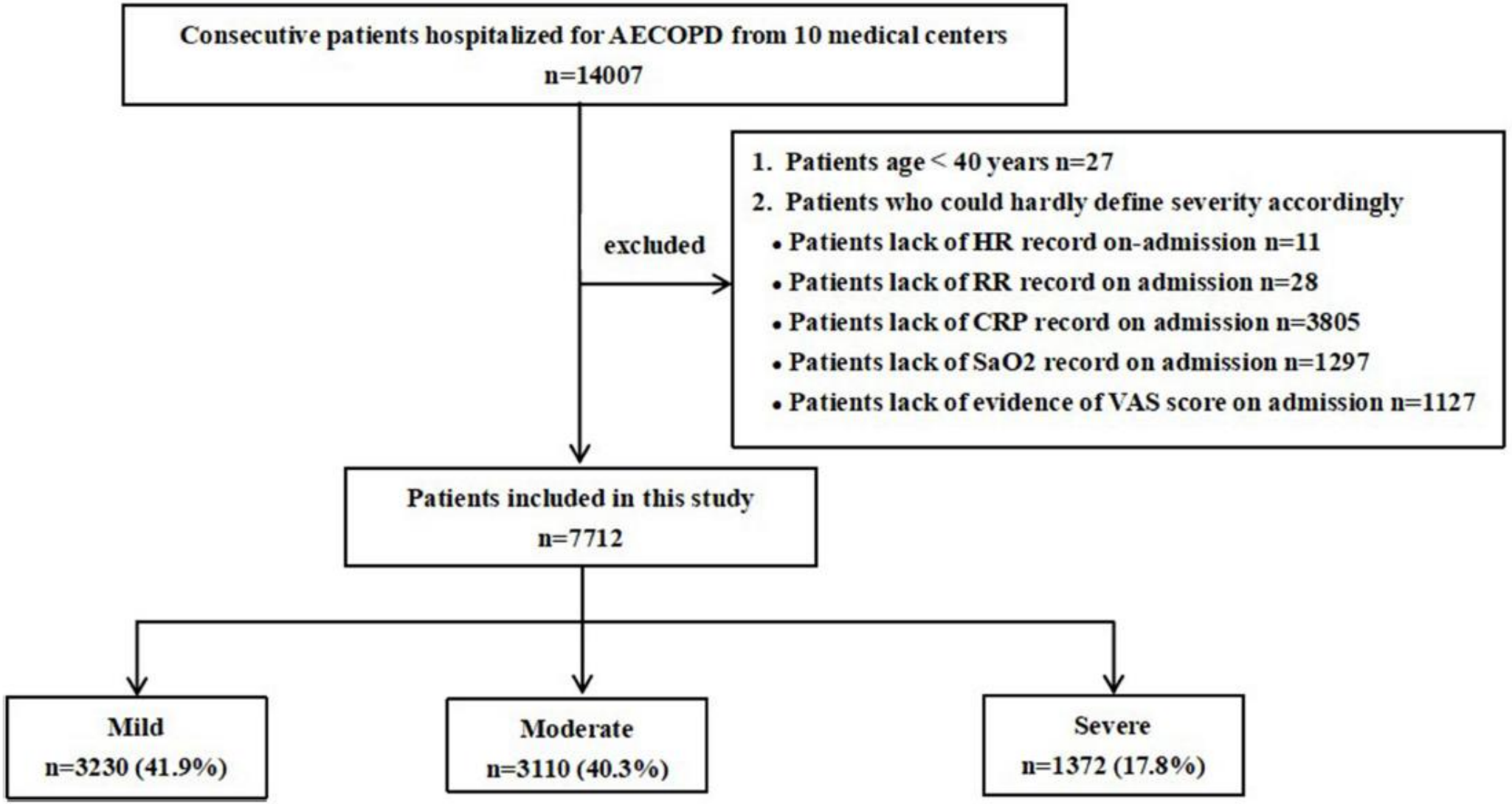
Int J Chron Obstruct Pulmon Dis 2024 Jan 17:19:193-204.

Rome severity classification of ECOPD



Int J Chron Obstruct Pulmon Dis 2024 Jan 17:19:193-204.

Rome severity classification of ECOPD

Table 4 Outcomes According to AECOPD Severity Based on the Rome Classification

Outcomes	Total (N=7712)	Mild (N=3230)	Moderate (N=3110)	Severe (N=1372)	P value*
In-hospital Mortality	151 (2.0%)	37 (1.1%)	80 (2.6%)	34 (2.5%)	**<0.001**
60-day Mortality after admission	242 (3.1%)	60 (1.9%)	134 (4.3%)	48 (3.5%)	**<0.001**
ICU admission	785 (10.2%)	208 (6.4%)	372 (12.0%)	205 (14.9%)	**<0.001**
Mechanical Ventilation	2000 (26.9%)	354 (11.7%)	1024 (33.7%)	622 (45.3%)	**<0.001**
Invasive Mechanical Ventilation	378 (4.9%)	45 (1.4%)	211 (6.8%)	122 (8.9%)	**<0.001**
Length of Stay (day)	10 (7)	10 (7)	10 (8)	9 (7)	**<0.001**
Glucocorticoid use (I.V. or Oral)	3183 (41.3%)	862 (26.7%)	1483 (47.7%)	838 (61.1%)	**<0.001**
Glucocorticoid use (I.V.)	2675 (34.7%)	672 (20.8%)	1209 (38.9%)	794 (57.9%)	**<0.001**
Anti-biotic use	6050 (78.5%)	2470 (76.5%)	2587 (83.2%)	993 (72.4%)	**<0.001**

Rome classification showed difference in ICU admission, need for MV

Int J Chron Obstruct Pulmon Dis 2024 Jan 17:19:193-204.

Validation of Rome proposal

THERAPEUTIC ADVANCES in
Respiratory Disease

Original Research

Validation of the Rome proposal for severity of acute exacerbation of chronic obstructive pulmonary disease

Ther Adv Respir Dis
2023, Vol. 17: 1–14
DOI: 10.1177/17534666231172917

Hyo Jin Lee, Jung-Kyu Lee, Tae Yun Park, Eun Young Heo, Deog Kyeom Kim and Hyun Woo Lee

Abstract

Background: The Rome proposal provides an objective assessment tool for severity of acute exacerbation of chronic obstructive pulmonary disease (AE-COPD) but requires validation.

Objectives: We aimed to evaluate the predictive performance of the Rome proposal in patients with AE-COPD.

Design: This observational study assessed the patients who visited the emergency room (ER) or were hospitalized due to AE-COPD between January 2010 and December 2020.

Methods: We compared the performance of the Rome Proposal with that of the DECAF score or GesEPOC 2021 criteria in predicting intensive care unit (ICU) admission, need for non-invasive ventilation (NIV) or invasive mechanical ventilation (IMV), and in-hospital mortality.

Results: A total of 740 events of ER visit or hospitalization due to AE-COPD were reviewed and classified into mild (30.9%), moderate (58.6%), or severe (10.4%) group according to the Rome proposal. The severe group had a higher rate of ICU admission, required more NIV or IMV, and had a higher in-hospital mortality than the mild and moderate groups. The predictive performance of the Rome proposal was significantly better for ICU admission [area under the receiver operating characteristic curve (AU-ROC) = 0.850 *versus* 0.736, $p = 0.004$] and need for NIV or IMV (AU-ROC = 0.870 *versus* 0.770, $p = 0.004$) than that of the GesEPOC 2021 criteria but better than that of the DECAF score only in female patients. There was no significant difference in predicting the in-hospital mortality between the Rome proposal and DECAF score or GesEPOC 2021 criteria.

Conclusion: External validation of the Rome Proposal in Korean patients demonstrated excellent performance for ICU admission and need for NIV or IMV and an acceptable performance for in-hospital mortality.

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Validation of Rome proposal

Table 3. Clinical outcomes according to AE-COPD severity based on the Rome proposal.

	Mild ($n = 229$, 30.9%)	Moderate ($n = 434$, 58.6%)	Severe ($n = 77$, 10.4%)	Total ($N = 740$)	p for linear trend	p
ICU admission, *n* (%)	0	9 (2.07)	19 (24.68)	28 (3.78)	<0.001	<0.001
ICU LOS, days, mean ± SD	0	0.1 ± 0.05	1.5 ± 0.4	0.2 ± 0.1	<0.001	<0.001
Hospital LOS, days, median (IQR)	5 (2–9)	7 (4–11)	8 (5–17)	6 (3–10)	0.169	<0.001
Oxygen delivery equipment						
Conventional oxygen therapy	55 (24.02)	237 (54.61)	56 (72.73)	348 (47.03)	<0.001	<0.001
High-flow nasal oxygen	0	6 (1.38)	3 (3.9)	9 (1.22)	0.008	0.023
Non-invasive ventilation	0	8 (1.84)	15 (19.48)	23 (3.11)	<0.001	<0.001
Mechanical ventilation	0	2 (0.46)	14 (18.18)	16 (2.16)	<0.001	<0.001
Reintubation	0	0 (0)	1 (1.3)	1 (0.14)	0.048	0.013
Tracheostomy	0	0 (0)	2 (2.6)	2 (0.27)	0.005	<0.001
In-hospital mortality	0	5 (1.15)	5 (6.49)	10 (1.35)	<0.001	<0.001

AE-COPD, acute exacerbation of chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; SD, standard deviation.
Data presented as *n* (%) or mean (SD) and median (IQR).

Validation of Rome proposal

Table 4. Prognostic accuracy of the Rome proposal, DECAF score, and GesEPOC 2021 criteria.

	Severity classification	Optimal cut-off	Sensitivity	Specificity	AU-ROC	95% CI
ICU admission	Rome proposal	Severe	0.679	0.919	0.850	0.789–0.911
	DECAF score	Intermediate	0.821	0.742	0.810	0.729–0.892
	GesEPOC 2021	Very high	0.321	0.985	0.736	0.657–0.814
NIV or IMV	Rome proposal	Severe	0.727	0.925	0.870	0.817–0.924
	DECAF score	Intermediate	0.818	0.745	0.801	0.726–0.875
	GesEPOC 2021	Very high	0.363	0.989	0.770	0.705–0.835
In-hospital mortality	Rome proposal	Severe	0.500	0.901	0.779	0.666–0.892
	DECAF score	Intermediate	0.700	0.726	0.738	0.573–0.903
	GesEPOC 2021	High	1.000	0.326	0.752	0.651–0.854

AU-ROC, area under the receiver operating characteristic curve; CI, confidence interval; DECAF, dyspnea with eMRCD (dyspnea with extended Medical Research Council dyspnea), eosinopenia, consolidation, acidemia, atrial fibrillation; GesEPOC, Spanish COPD Guidelines; ICU, intensive care unit; IMV, invasive mechanical ventilation; NIV, non-invasive ventilation.

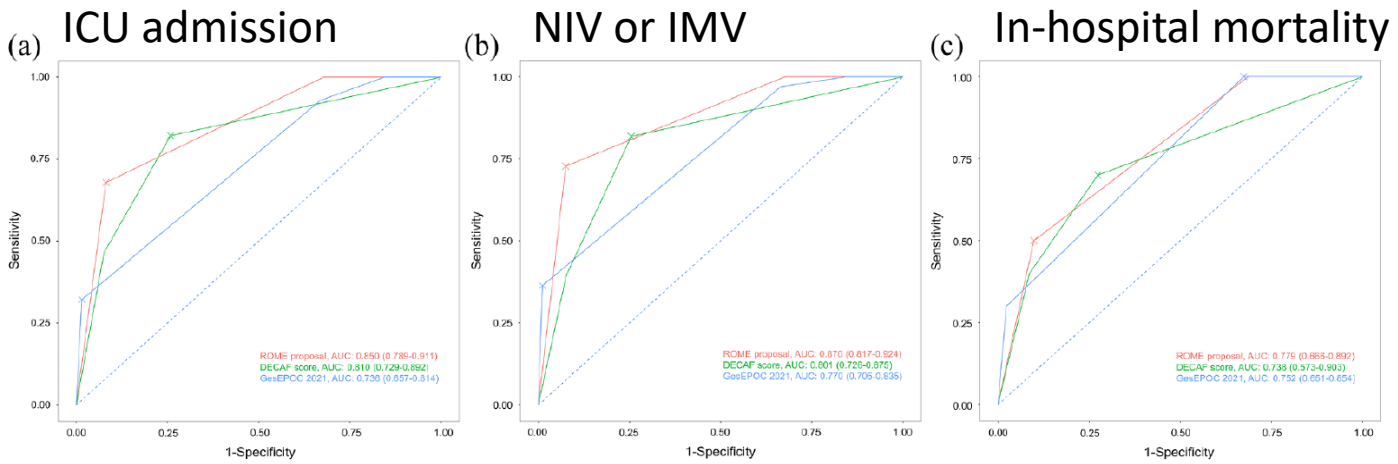

Figure 2. ROC curve of Rome proposal, DECAF score, and GesEPOC 2021 criteria: (a) Delong's tests for ICU admission: the Rome

Definition and classification of ECOPD ; Year-in-review 2024

- The ROME proposal has been adopted and studies have been published to classify patients with ECOPD and validate the criteria.
- The ROME proposal focuses on the classification and diagnosis of ECOPD as mild, moderate or severe using objective markers such as vital signs and inflammatory markers.
- We expect this concept to be applied to clinical trials in COPD patients in the future.

Diagnosis of ECOPD

Exacerbations: Diagnosis and Assessment

Figure 4.2

1.	Complete a thorough clinical assessment for evidence of COPD and potential respiratory and non-respiratory concomitant diseases, including consideration of alternative causes for the patient's symptoms and signs: primarily pneumonia, heart failure, and pulmonary embolism.
2.	**Assess:** a. Symptoms, severity of dyspnea that can be determined by using a VAS, and documentation of the presence of cough. b. Signs (tachypnea, tachycardia), sputum volume and color, and respiratory distress (accessory muscle use).
3.	Evaluate severity by using appropriate additional investigations such as pulse oximetry, laboratory assessment, CRP, arterial blood gases.
4.	Consider appropriate place of care.
5.	Establish the cause of the event (viral, bacterial, environmental, other).

Abbreviations: COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; VAS = visual analog scale.

Differential diagnosis of ECOPD in acute care setting

CONCISE CLINICAL REVIEW

Differential Diagnosis of Suspected Chronic Obstructive Pulmonary Disease Exacerbations in the Acute Care Setting

Best Practice

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Am J Respir Crit Care Med. 2023 May 1;207(9):1134-1144.

Differential diagnosis of ECOPD in acute care setting

Table 1. The CASE (Complete, Assess, Severity, Establish) Approach to a Patient with Confirmed or Suspected Chronic Obstructive Pulmonary Disease Who Presents with Worsening Respiratory Symptoms

Complete	A thorough clinical assessment for evidence of underlying COPD and potential respiratory and nonrespiratory concomitant diseases, including consideration of alternative causes for the patient's symptoms and signs
Assess	Symptoms: Severity of dyspnea using a tool such as the dyspnea visual analog scale; documentation of the presence and characteristics of cough and sputum. Presence of pain and its characteristics Signs: Tachypnea, tachycardia, arrhythmia, fever, sputum volume and color, respiratory distress (accessory muscle usage), abnormalities on thoracic examination, and thorough physical examination
Severity	Evaluate by combining symptoms and signs and appropriate additional investigations such as pulse oximetry. If available, obtain laboratory assessments (e.g., CRP), chest X-ray, electrocardiograph, and/or arterial blood gases
Establish	Cause of the event (viral, bacterial, environmental, poor treatment adherence, alternative diagnosis, or other)

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein.

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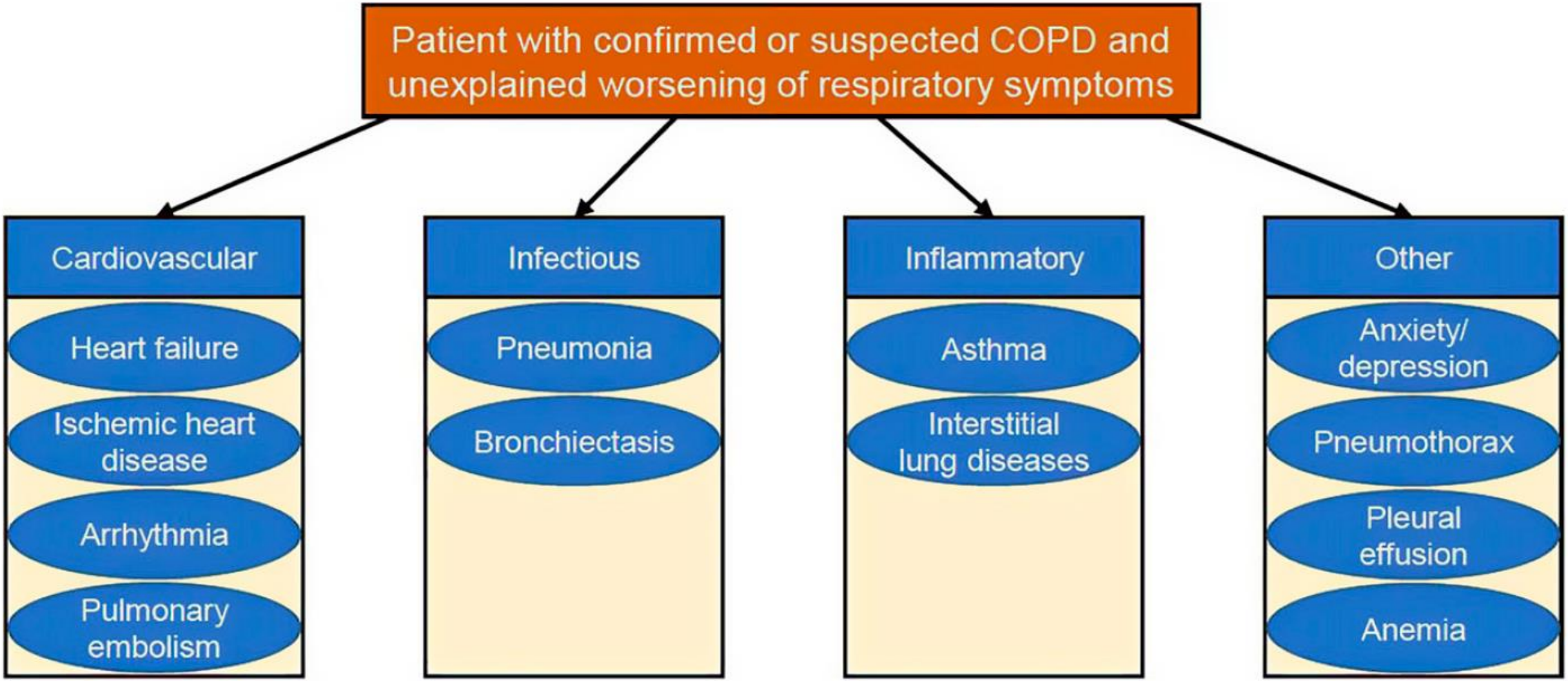
Differential diagnosis of ECOPD in acute care setting



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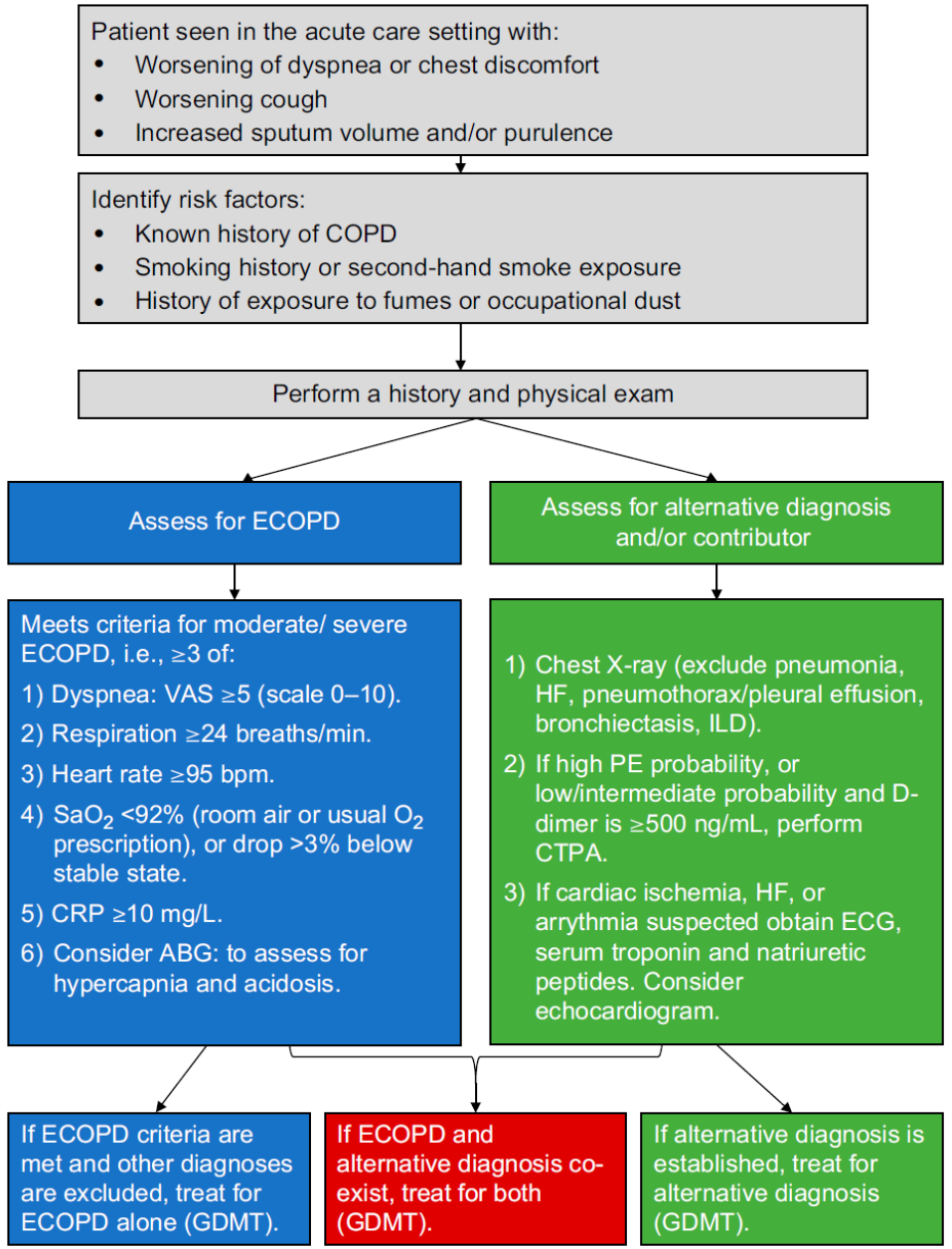
Differential diagnosis of ECOPD in acute care setting



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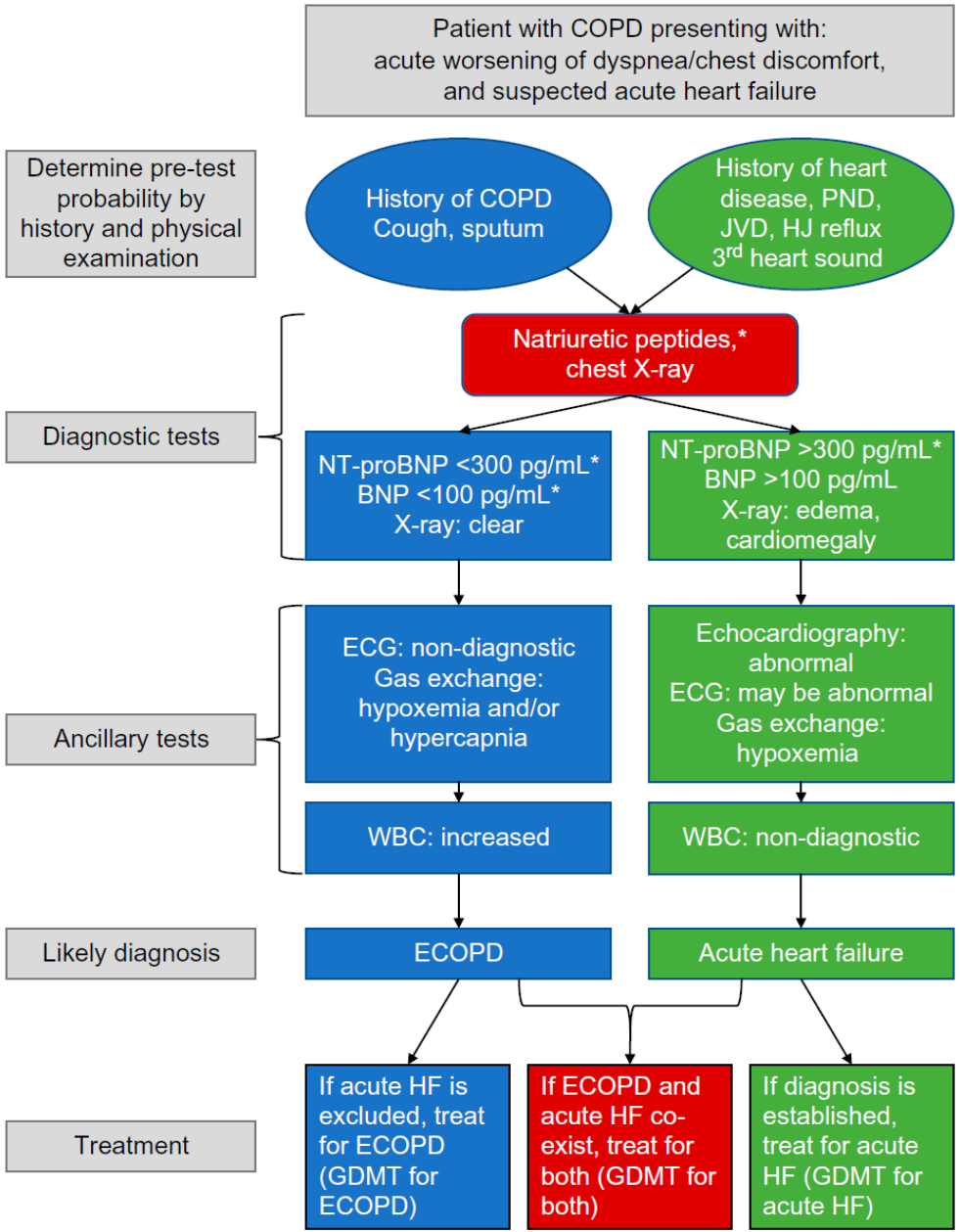
Differential diagnosis of ECOPD in acute care setting



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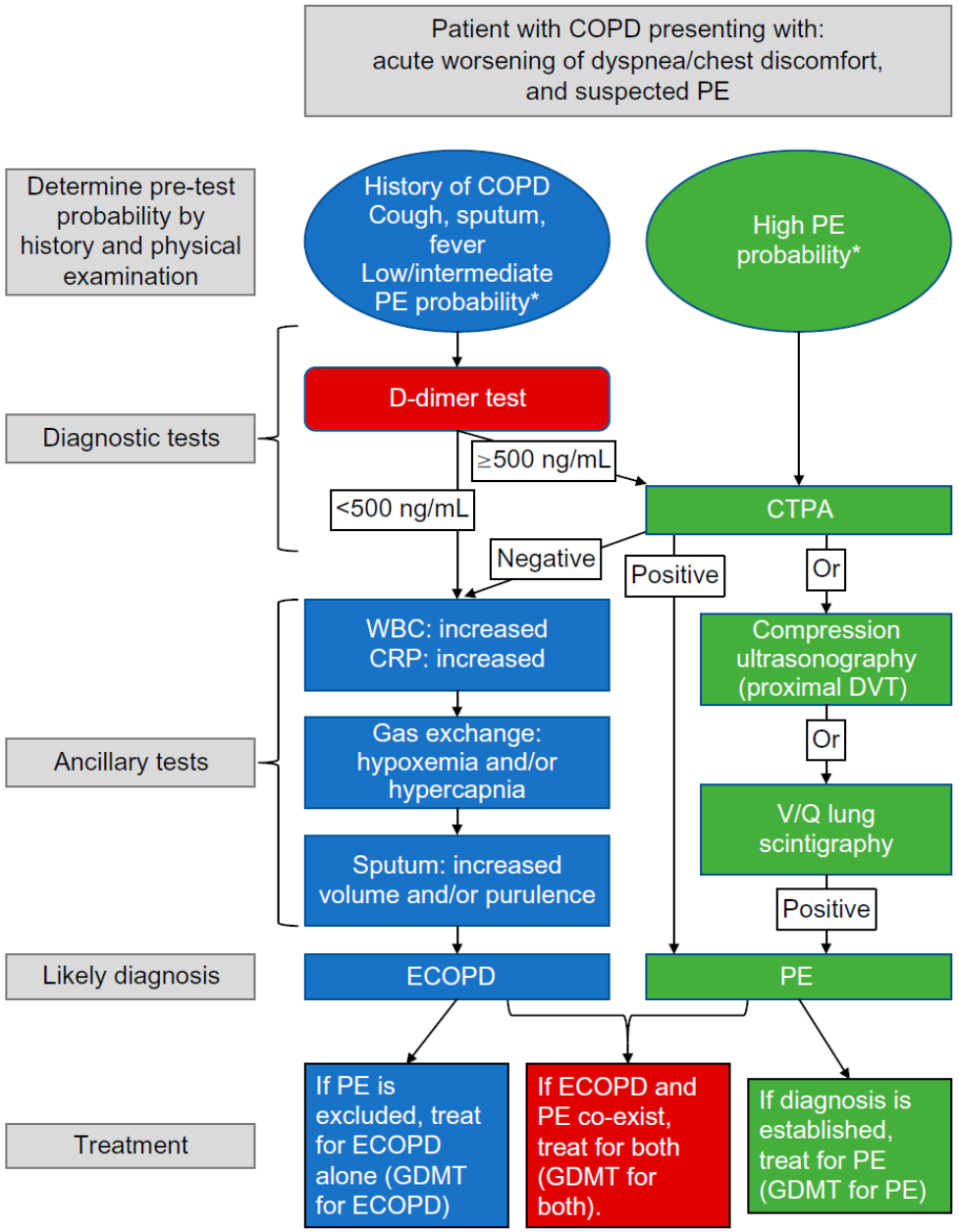
Differential diagnosis of ECOPD in acute care setting



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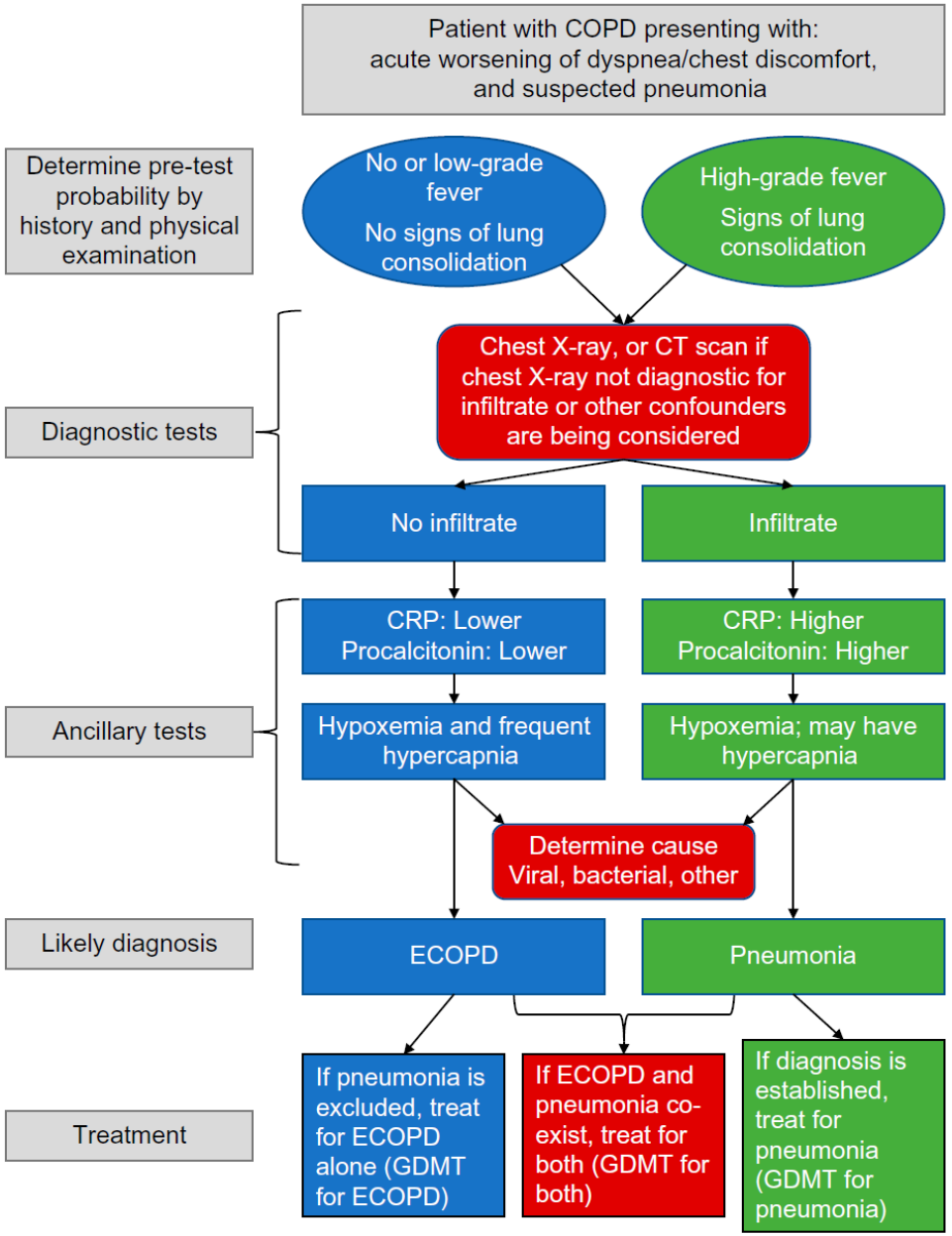
Differential diagnosis of ECOPD in acute care setting

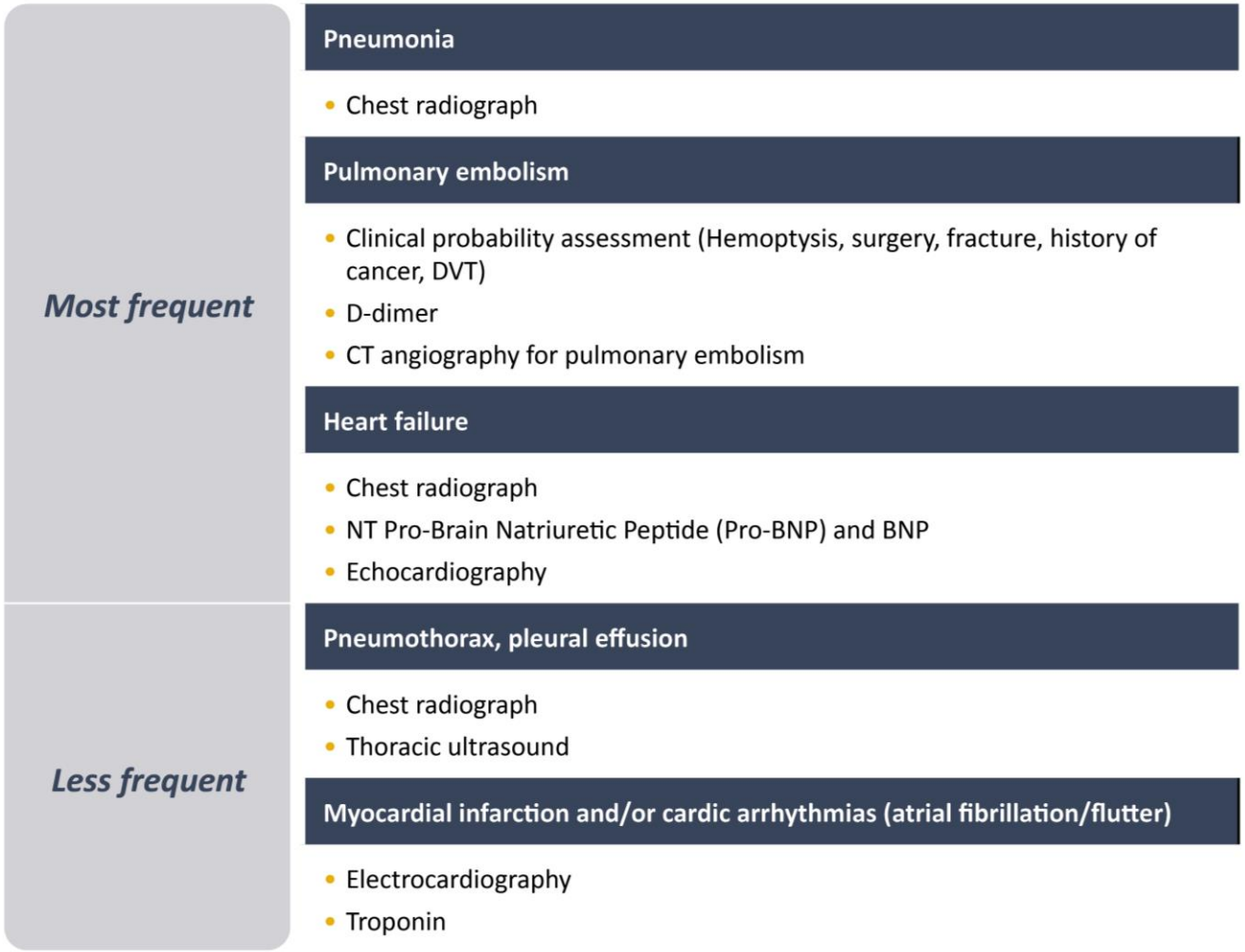


Am J Respir Crit Care Med. 2023 May 1;207(9):1134-1144.

Diagnosis of ECOPD

Confounders or Contributors to be Considered in Patients Presenting with Suspected COPD Exacerbation

Figure 4.1



Management of ECOPD

Key Points for the Management of Exacerbations

Figure 4.6

- Short-acting inhaled beta$_2$-agonists, with or without short-acting anticholinergics, are recommended as the initial bronchodilators to treat an acute exacerbation **(Evidence C)**
- Systemic corticosteroids can improve lung function (FEV1), oxygenation and shorten recovery time and hospitalization duration. Duration of therapy should not normally be more than 5 days **(Evidence A)**
- Antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospitalization duration. Duration of therapy should normally be 5 days **(Evidence B)**
- Methylxanthines are not recommended due to increased side effect profiles **(Evidence B)**
- Non-invasive mechanical ventilation should be the first mode of ventilation used in COPD patients with acute respiratory failure who have no absolute contraindication because it improves gas exchange, reduces work of breathing and the need for intubation, decreases hospitalization duration and improves survival **(Evidence A)**

Management of ECOPD ; Year-in-review 2024

- Pharmacological approaches
  - Administration of systemic steroid
  - Nebulised interferon beta-1a
- Non-pharmacological approaches
  - High flow nasal cannula
  - NIV

STARR2 trial

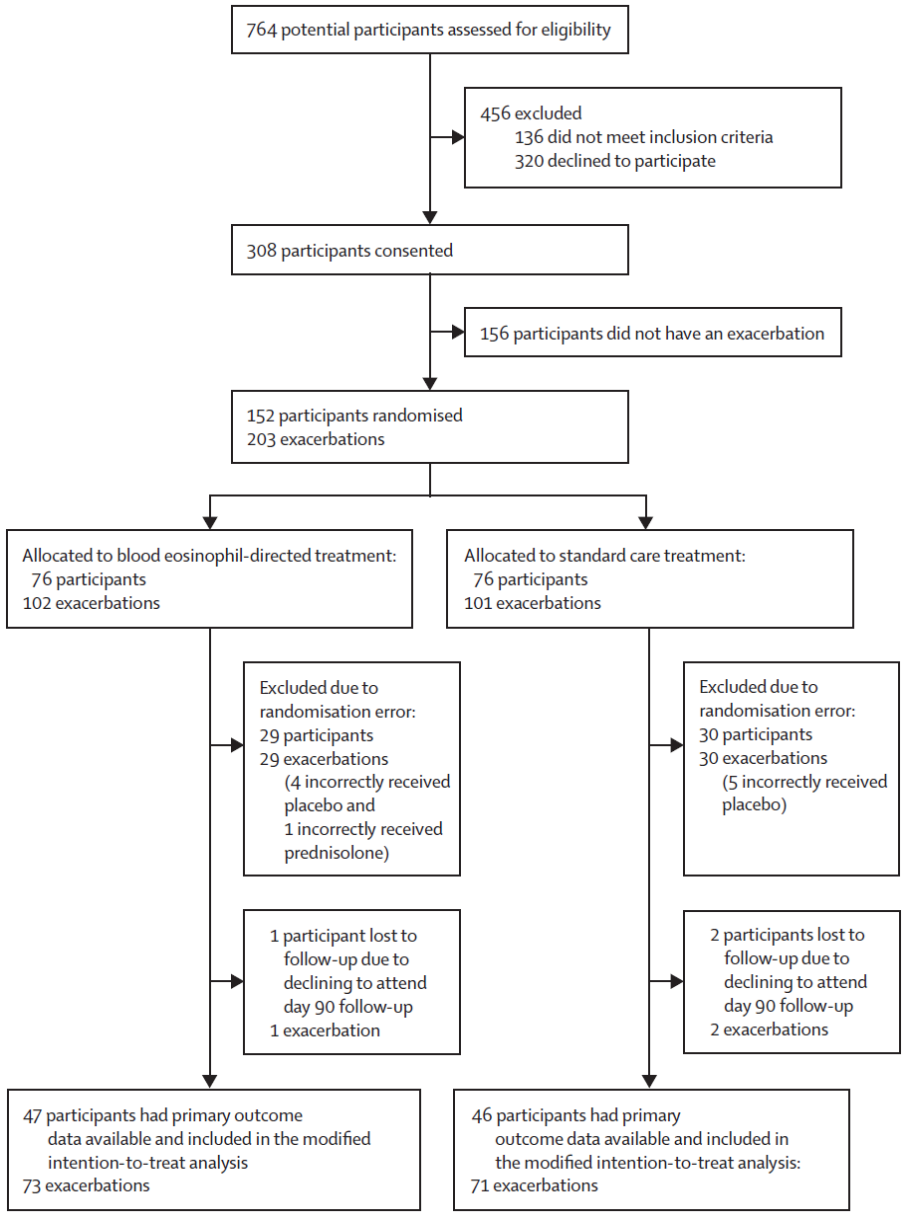
Articles

Blood eosinophil-guided oral prednisolone for COPD exacerbations in primary care in the UK (STARR2): a non-inferiority, multicentre, double-blind, placebo-controlled, randomised controlled trial

Sanjay Ramakrishnan, Helen Jeffers, Beverly Langford-Wiley, Joanne Davies, Samantha J Thulborn, Mahdi Mahdi, Christine A'Court, Ian Binnian, Stephen Bright, Simon Cartwright, Victoria Glover, Alison Law, Robin Fox, Adam Jones, Christopher Davies, David Copping, Richard EK Russell, Mona Bafadhel

Lancet Respir Med 2024; 12: 67–77

STARR2 trial



Lancet Respir Med 2024; 12: 67–77

STARR2 trial – study design

The studying acute exacerbations and response (STARR2)
Multicenter, randomized, double-blind study conducted in 14 primary care

- P : COPD group E
- I : **Blood eosinophil-directed treatment (BET; oral PD 30 mg once daily if eosinophil count was high [≥2%] or placebo if eosinophil count was low [<2%], for 14 days)**
- C : Standard care treatment (ST; to receive prednisolone 30 mg once daily irrespective of the point-of-care eosinophil result, for 14 days)
- O : Rate of treatment failure, defined as any need for re-treatment with antibiotics or steroids, hospitalisation for any cause, or death, assessed at 30 days after exacerbation

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Pharmacological management of ECOPD

	Standard care treatment group (n=46)	Blood eosinophil-directed group treatment (n=47)
Sex		
Female	20 (43%)	21 (45%)
Male	26 (57%)	26 (55%)
Mean age, years	70 (range 46–83)	70 (range 50–84)
Smoker status		
Current smoker	7 (15%)	16 (34%)
Former smoker	39 (85%)	31 (66%)
Mean smoked pack years	50 (range 10–140)	60 (range 10–175)
Comorbidity		
Any	45 (98%)	46 (98%)
Hypertension	23 (50%)	22 (47%)
Gastro-oesophageal reflux	16 (35%)	20 (43%)
Depression	13 (28%)	17 (36%)
History of malignancy	7 (15%)	10 (21%)
Ischaemic heart disease	11 (24%)	8 (17%)
Diabetes	4 (9%)	7 (15%)
Atrial fibrillation	7 (15%)	7 (15%)
Osteoporosis	2 (4%)	4 (9%)
Cerebrovascular disease	1 (2%)	1 (2%)
Heart failure	0	4 (9%)
BMI, kg/m²	27·9 (6·2)	28·2 (6·2)
FEV_1, L	1·60 (0·62)	1·51 (0·62)
FEV_1, % predicted	61·0 (19·4)	60·8 (19·2)
FEV_1/FVC	0·55 (0·10)	0·56 (0·10)
COPD Assessment Test score	14 (7)	16 (7)
VAS total, mm*	119 (95)	162 (118)
VAS cough, mm	24 (21)	34 (26)
VAS dyspnoea, mm	29 (25)	40 (25)
VAS sputum production, mm	22 (23)	28 (28)
VAS sputum purulence, mm	20 (22)	28 (29)
VAS wheeze, mm	23 (23)	31 (27)
Median EuroQOL level sum score	6 (IQR 5–8)	7 (IQR 5–8)
Median hospital anxiety and depression score	9 (IQR 5–13)	12 (IQR 5–16)
Median number of previous exacerbations in past 12 months	2 (IQR 1–3)	2 (IQR 1–3)
Treatment		
On long-acting muscarinic antagonist therapy	28 (61%)	27 (57%)
On long-acting β2-receptor agonist therapy	30 (65%)	26 (55%)
On inhaled glucocorticoid therapy†	28 (61%)	26 (55%)
Beclomethasone dipropionate equivalent, µg	567 (578)	572 (576)
Median Medical Research Council score	2 (IQR 2–3)	3 (IQR 2–3)
Geometric mean leukocytes (95% CI), 10^9 cells per L	7·02 (6·49–7·47)	6·99 (6·85–8·18)
Geometric mean neutrophils (95% CI), 10^9 cells per L	4·24 (3·83–4·66)	4·24 (4·06–4·98)
Geometric mean eosinophils (95% CI), 10^9 cells per L	0·16 (0·14–0·20)	0·16 (0·14–0·20)
Median C-reactive protein, g/L	5 (IQR 2–8)	6 (IQR 2–10)

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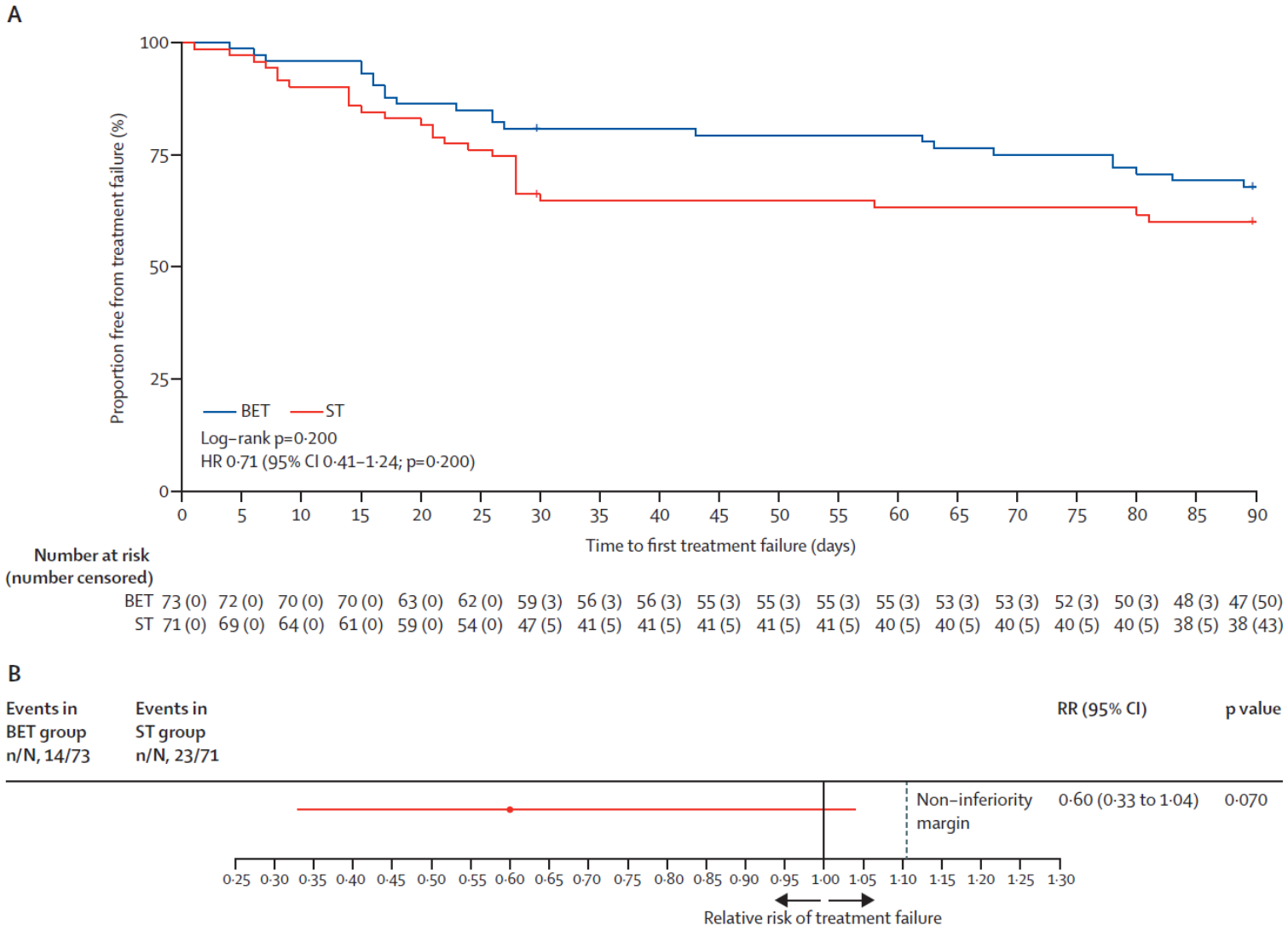
STARR2 trial – primary outcome



The non-inferiority analysis supported that BET was non-inferior to ST.

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STARR2 trial – secondary analysis

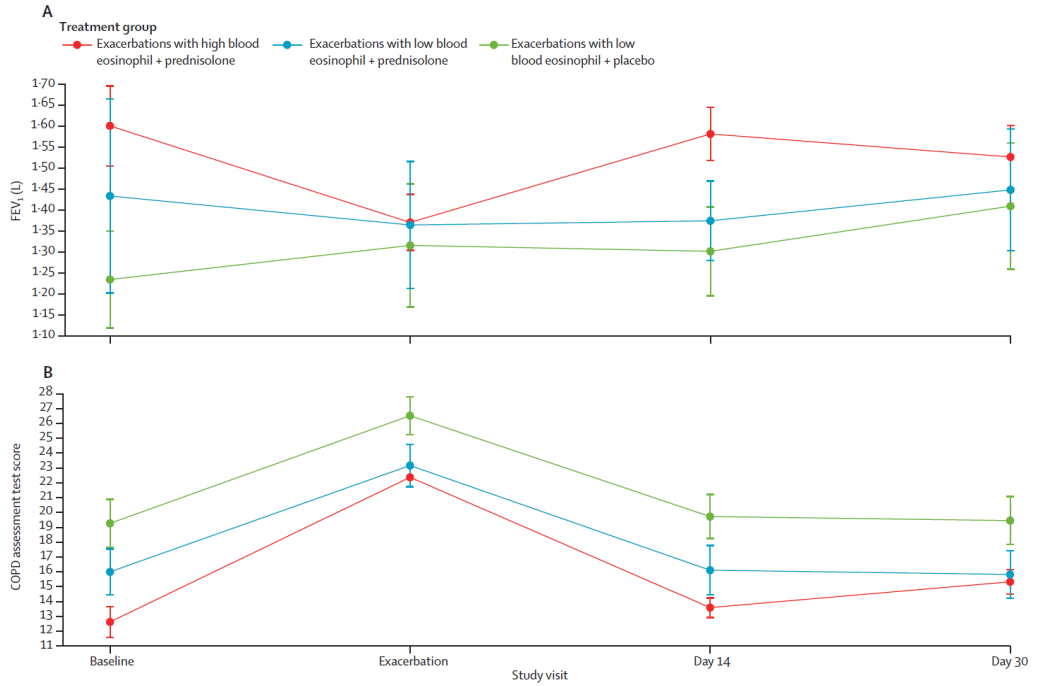
	Standard care treatment group (n=71)	Blood eosinophil-directed group (n=73)	p value
Change in COPD Assessment Test score	7 (6 to 8)	8 (6 to 10)	0·271
Change in FEV_1, L	0·14 (0·07 to 0·21)	0·17 (0·10 to 0·24)	0·548
Change in VAS total, mm*	126 (99 to 152)	127 (103 to 150)	0·971
Change in VAS cough, mm	25 (19 to 31)	26 (20 to 32)	0·828
Change in VAS dyspnoea, mm	22 (15 to 29)	23 (17 to 29)	0·772
Change in VAS sputum production, mm	26 (19 to 33)	24 (18 to 30)	0·726
Change in VAS sputum purulence, mm	26 (18 to 34)	25 (19 to 31)	0·857
Change in VAS wheeze, mm	27 (21 to 33)	26 (21 to 32)	0·933
Geometric mean change in leukocytes (95% CI), 10^9 cells per L	2·7 (1·5 to 3·9)	1·7 (0·9 to 2·5)	0·167
Geometric mean change in neutrophils (95% CI), 10^9 cells per L	1·8 (0·9 to 2·7)	1·3 (0·7 to 1·9)	0·313
Geometric mean change in eosinophils (95% CI), 10^9 cells per L	−0·2 (−0·3 to −0·1)	−0·2 (−0·2 to −0·1)	0·535
Median Change in C-reactive protein, g/L	−10 (IQR −32 to −4)	−5 (IQR −15 to −3)	0·058

Data are mean (95% CI) unless otherwise stated. A negative value in FEV_1, COPD Assessment Test score, and VAS indicates worsening (reduction). COPD=chronic obstructive pulmonary disease. VAS=visual analogue scale. *VAS total is the total of each of the VAS domains.

Table 2: **Secondary analysis of the difference in clinical, physiological, and biological characteristics after treatment allocation between exacerbation (randomisation) and 2 weeks of treatment (day 14 follow-up visit) in modified intention-to-treat population**

Lancet Respir Med 2024; 12: 67–77

STARR2 trial – secondary analysis



er at risk ensored) nt group																			
ions with osinophil lnisolone	94 (0)	92 (0)	90 (0)	89 (0)	84 (0)	79 (0)	71 (6)	64 (6)	64 (6)	63 (6)	63 (6)	63 (6)	62 (6)	61 (6)	60 (6)	60 (6)	59 (6)	55 (6)	54 (60)
ions with osinophil + placebo	24 (0)	24 (0)	22 (0)	22 (0)	20 (0)	20 (0)	20 (1)	19 (1)	19 (1)	19 (1)	19 (1)	19 (1)	18 (1)	18 (1)	18 (1)	18 (1)	17 (1)	17 (1)	17 (18)
ions with osinophil lnisolone	26 (0)	25 (0)	22 (0)	20 (0)	18 (0)	17 (0)	15 (1)	14 (1)	14 (1)	14 (1)	14 (1)	14 (1)	14 (1)	14 (1)	14 (1)	14 (1)	14 (1)	14 (1)	14 (15)

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Nebulised interferon beta-1a

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https://doi.org/10.1186/s12931-024-02854-7

Respiratory Research

RESEARCH Open Access

Nebulised interferon beta-1a (SNG001) in the treatment of viral exacerbations of COPD

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Abstract

Background Respiratory viral infections are major drivers of chronic obstructive pulmonary disease (COPD) exacerbations. Interferon-β is naturally produced in response to viral infection, limiting replication. This exploratory study aimed to demonstrate proof-of-mechanism, and evaluate the efficacy and safety of inhaled recombinant interferon-β1a (SNG001) in COPD. Part 1 assessed the effects of SNG001 on induced sputum antiviral interferon-stimulated gene expression, sputum differential cell count, and respiratory function. Part 2 compared SNG001 and placebo on clinical efficacy, sputum and serum biomarkers, and viral clearance.

Methods In Part 1, patients ($N=13$) with stable COPD were randomised 4:1 to SNG001 or placebo once-daily for three days. In Part 2, patients ($N=109$) with worsening symptoms and a positive respiratory viral test were randomised 1:1 to SNG001 or placebo once-daily for 14 days in two Groups: A (no moderate exacerbation); B (moderate COPD exacerbation [i.e., acute worsening of respiratory symptoms treated with antibiotics and/or oral corticosteroids]).

Results In Part 1, SNG001 upregulated sputum interferon gene expression. In Part 2, there were minimal SNG001–placebo differences in the efficacy endpoints; however, whereas gene expression was initially upregulated by viral infection, then declined on placebo, levels were maintained with SNG001. Furthermore, the proportion of patients with detectable rhinovirus (the most common virus) on Day 7 was lower with SNG001. In Group B, serum C-reactive protein and the proportion of patients with purulent sputum increased with placebo (suggesting bacterial infection), but not with SNG001. The overall adverse event incidence was similar with both treatments.

Conclusions Overall, SNG001 was well-tolerated in patients with COPD, and upregulated lung antiviral defences to accelerate viral clearance. These findings warrant further investigation in a larger study.

Trial registration EU clinical trials register (2017-003679-75), 6 October 2017.

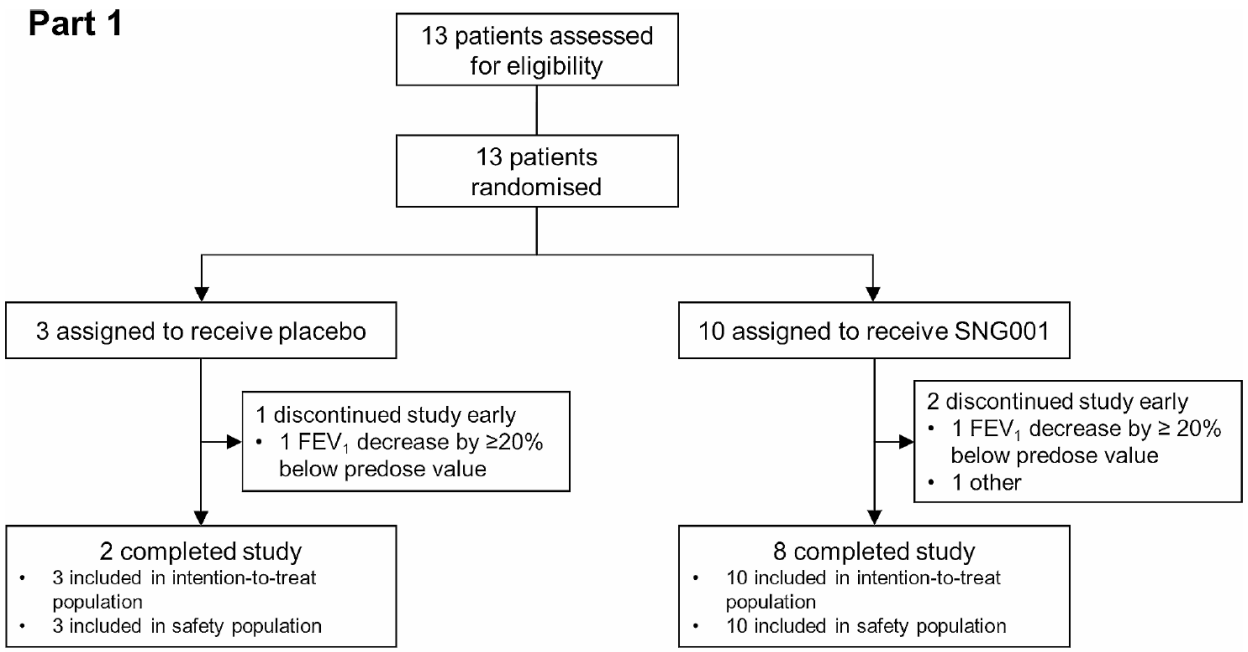
Keywords Chronic obstructive pulmonary disease, Symptom flare up, Interferons, Biomarkers

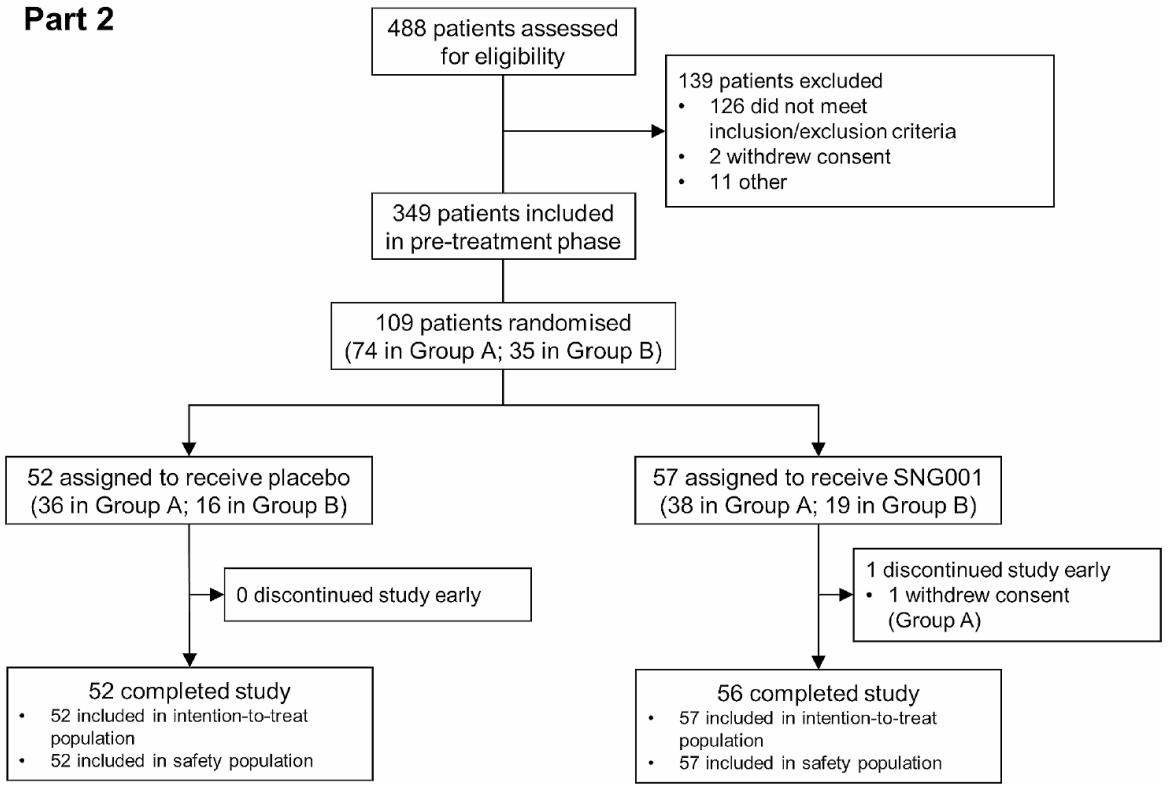
Nebulised IFN-beta

- P : part 1 - stable COPD
  part 2 – worsening symptoms and URI
- I : SNG001 (interferon beta)
- C : placebo
- O : part 1 – sputum interferon expression
  part 2 – BCSS total score change

Respir Res. 2024 May 29;25(1):228

Nebulised interferon beta-1a : study design





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Nebulised interferon beta-1a : baseline characteristics

Table 1 Patient baseline demographics and disease characteristics

	Part 1		Part 2			
			Group A (cold-like symptoms and/or deterioration in COPD symptoms)		Group B (moderate COPD exacerbation)	
	Placebo (*N* = 3)	SNG001 (*N* = 10)	Placebo (*N* = 36)	SNG001 (*N* = 38)	Placebo (*N* = 16)	SNG001 (*N* = 19)
Age, years	67.7 (NC)	67.1 (5.13)	64.6 (6.52)	66.9 (7.14)	66.8 (8.75)	67.2 (7.71)
Sex, male	2 (66.7%)	7 (70.0%)	22 (61.1%)	24 (63.2%)	9 (56.3%)	10 (52.6%)
BMI, kg/m^2	26.0 (NC)	29.5 (6.01)	28.7 (5.98)	29.0 (6.39)	28.5 (5.12)	28.4 (6.24)
Race						
White	3 (100%)	10 (100%)	33 (91.7%)	35 (92.1%)	16 (100%)	19 (100%)
Smoking status						
Current smoker	2 (66.7%)	1 (10.0%)	17 (47.2%)	15 (39.5%)	4 (25.0%)	6 (31.6%)
Former smoker	1 (33.3%)	9 (90.0%)	19 (52.8%)	23 (60.5%)	12 (75.0%)	13 (68.4%)
Smoking pack-years	40.3 (NC)	38.1 (14.39)	43.0 (23.49)	51.0 (30.36)	48.8 (17.73)	52.2 (20.28)
CAT total score	22.0 (NC)	19.7 (5.12)	19.8 (8.38)	20.4 (6.28)	21.0 (8.88)	24.3 (6.31)
Post-bronchodilator FEV_1						
L	1.83 (NC)	1.74 (0.394)	1.71 (0.568)	1.64 (0.549)	1.56 (0.348)	1.63 (0.599)
% predicted	70.3 (NC)	62.0 (11.11)	58.4 (13.74)	59.6 (15.05)	58.1 (16.13)	61.7 (19.46)
Post-bronchodilator PEF, L/min	352.0 (NC)	355.3 (78.74)	329.8 (113.65)	310.4 (108.81)	295.7 (64.42)	301.9 (120.26)
Exacerbations in previous 12 months						
0	1 (33.3%)	5 (50.0%)	0	0	0	0
1	1 (33.3%)	4 (40.0%)	18 (50.0%)	14 (36.8%)	7 (43.8%)	6 (31.6%)
≥ 2	1 (33.3%)	1 (10.0%)	18 (50.0%)	24 (63.2%)	9 (56.3%)	13 (68.4%)
BCSS total score	–	–	5.8 (3.02)	6.8 (2.39)	7.9 (2.77)	7.9 (2.46)
Concurrent COPD medication						
Long-acting muscarinic antagonists	3 (100%)	8 (80.0%)	33 (91.7%)	29 (76.3%)	15 (93.8%)	17 (89.5%)
Long-acting β_2-agonists	3 (100%)	9 (90.0%)	32 (88.9%)	35 (92.1%)	14 (87.5%)	19 (100%)
Inhaled corticosteroids	3 (100%)	8 (80.0%)	28 (77.8%)	31 (81.6%)	14 (87.5%)	16 (84.2%)

Data are mean (SD) or n (%). COPD, chronic obstructive pulmonary disease; NC, not calculated (note that SDs were not calculated when data were available for ≤3 patients); BMI, body-mass index; CAT, COPD Assessment Test; FEV_1, forced expiratory volume in 1 s; PEF, peak expiratory flow; BCSS, Breathlessness, Cough and Sputum Scale

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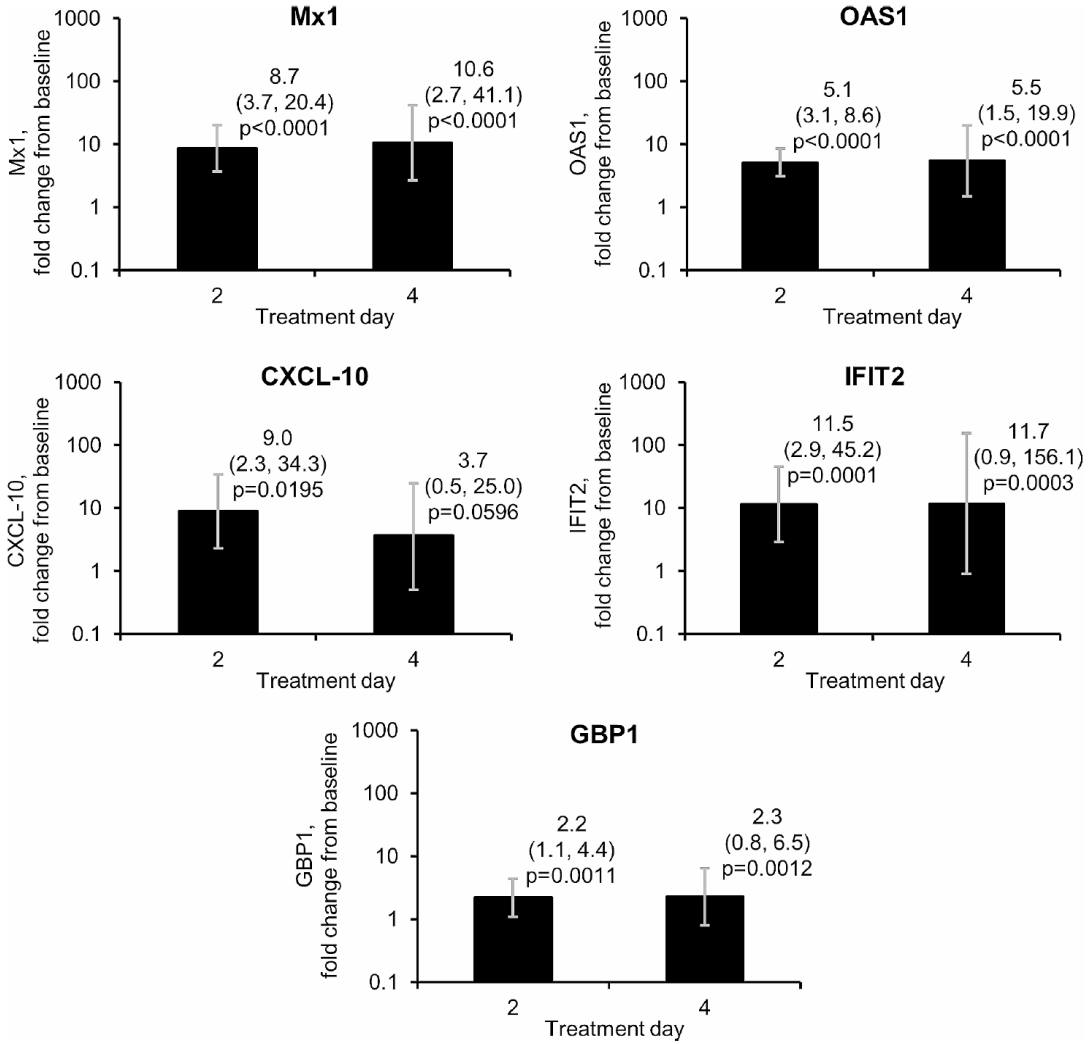
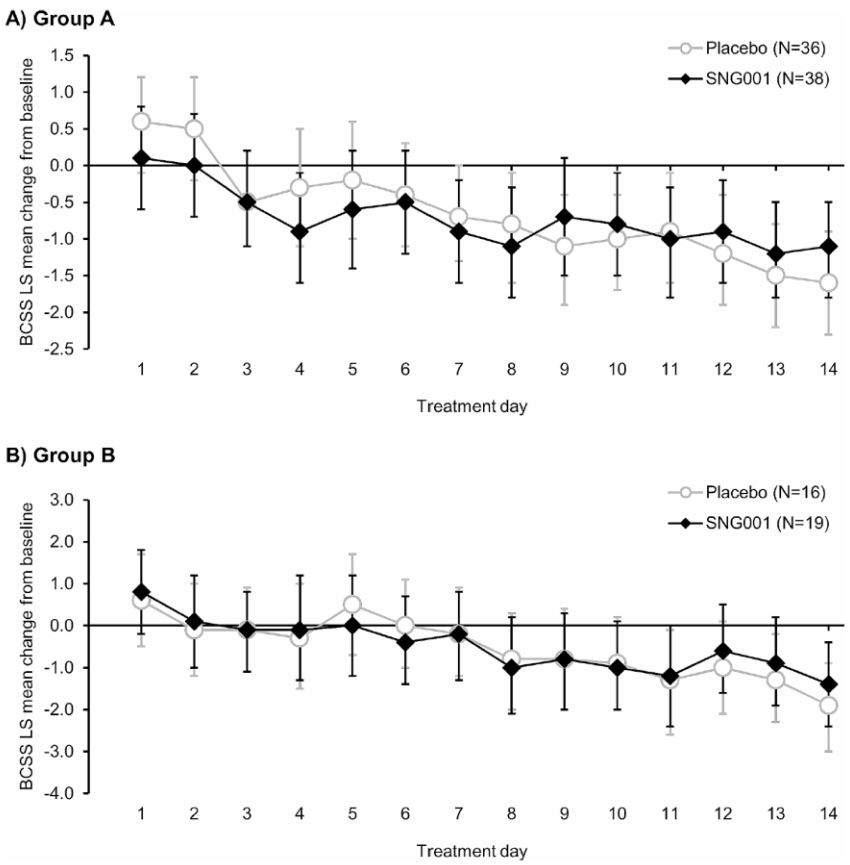
Part 1: Antiviral interferon-stimulated sputum gene expression following administration of SNG001

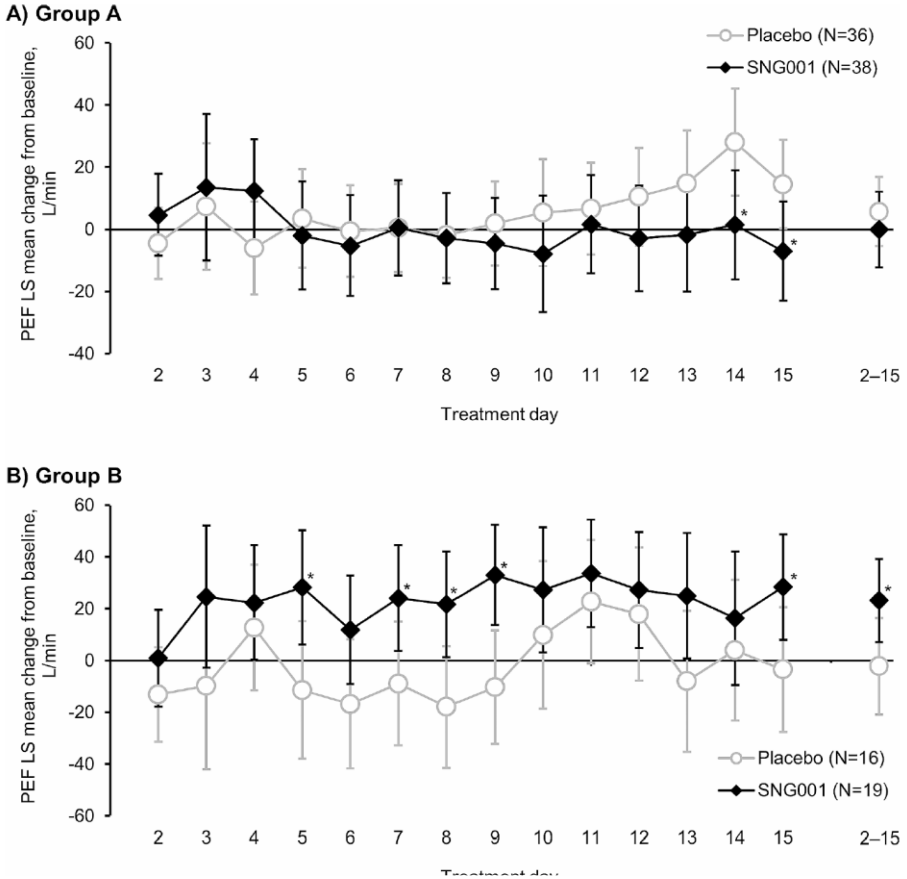


Part 2; primary and secondary outcomes

BCSS total scores



Home assessed PEF change from baseline



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Part 2; Detected viruses and viral clearance

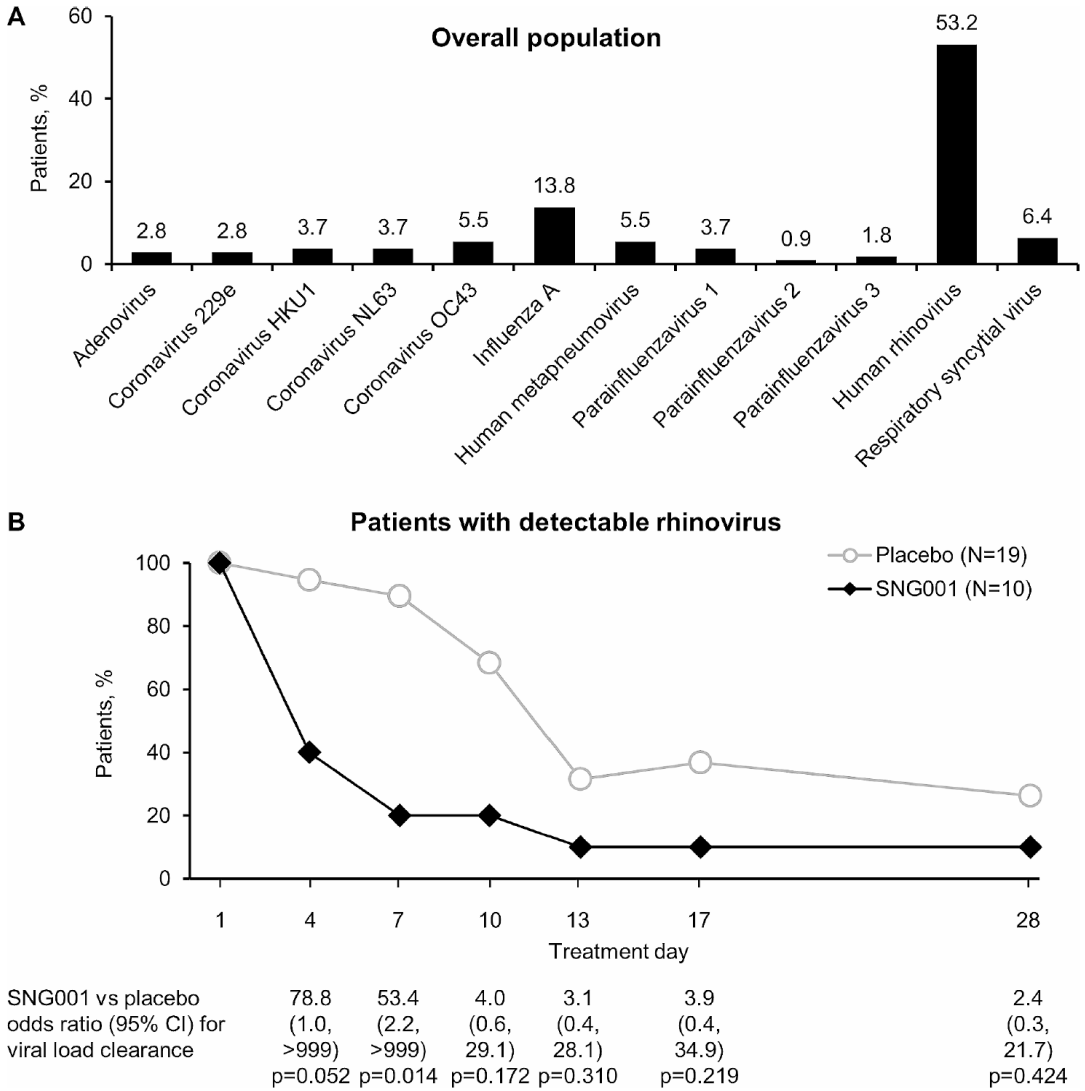

Fig. 5 Part 2: (**A**) Summary of baseline positive respiratory virus test results in the overall population; (**B**) Proportion of patients with detectable viral load for rhinovirus at baseline who had detectable rhinovirus viral load at each visit (ITT population)
Panel A: Note that patients could test positive for more than one respiratory virus. Panel B: N values are the number of patients with detectable viral load for rhinovirus at baseline

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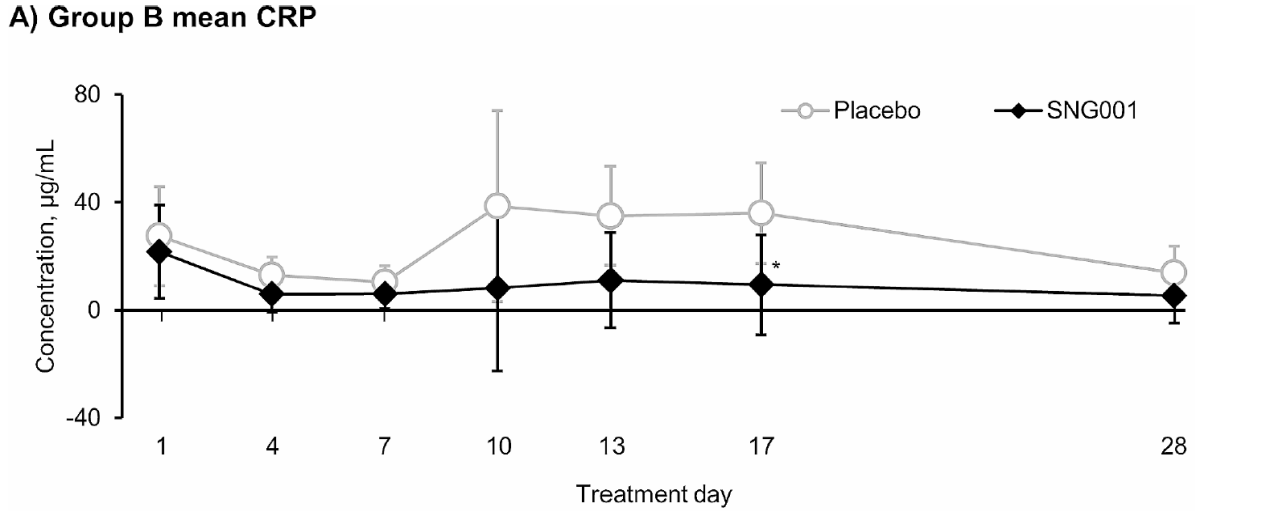
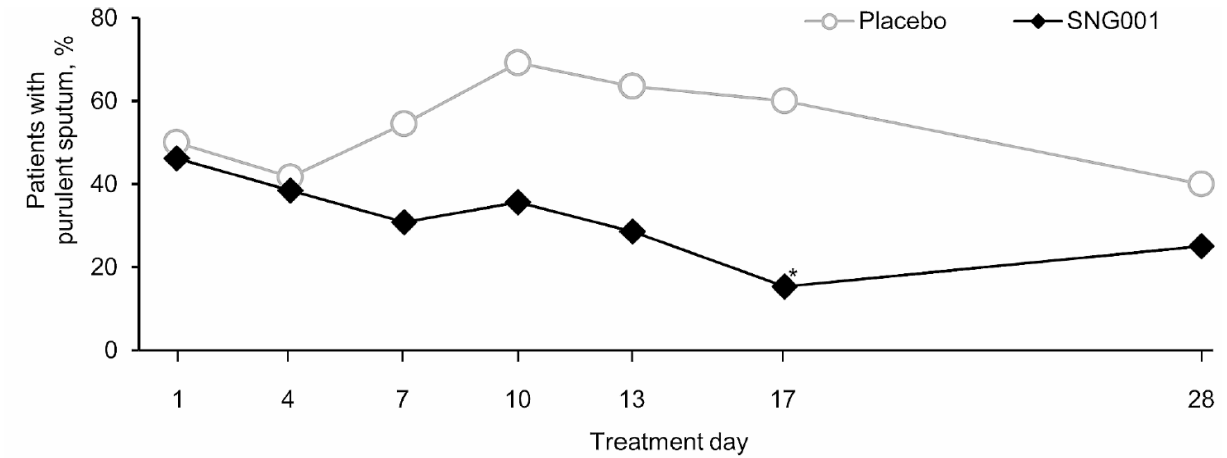
Part 2; CRP changes and proportion of patients with purulent sputum





Placebo	6/12	5/12	6/11	9/13	7/11	6/10	4/10
SNG001 (n/N)	6/13	5/13	4/13	5/14	4/14	2/13	3/12

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Indications for Noninvasive Mechanical Ventilation (NIV)

Figure 4.8

At least one of the following:

- Respiratory acidosis ($PaCO_2 \geq 6.0$ kPa or 45 mmHg and arterial pH ≤ 7.35)
- Severe dyspnea with clinical signs suggestive of respiratory muscle fatigue, increased work of breathing, or both, such as use of respiratory accessory muscles, paradoxical motion of the abdomen, or retraction of the intercostal spaces
- Persistent hypoxemia despite supplemental oxygen therapy

Nonpharmacological management of ECOPD

JAMA | Original Investigation

Effect of High-Intensity vs Low-Intensity Noninvasive Positive Pressure Ventilation on the Need for Endotracheal Intubation in Patients With an Acute Exacerbation of Chronic Obstructive Pulmonary Disease
The HAPPEN Randomized Clinical Trial

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IMPORTANCE The effect of high-intensity noninvasive positive pressure ventilation (NPPV) on the need for endotracheal intubation in patients with an acute exacerbation of chronic obstructive pulmonary disease (COPD) is unknown.

OBJECTIVE To determine whether the use of high-intensity NPPV vs low-intensity NPPV reduces the need for endotracheal intubation in patients with an acute exacerbation of COPD and hypercapnia.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial conducted at 30 general respiratory non–intensive care unit wards of Chinese hospitals from January 3, 2019, to January 31, 2022; the last 90-day follow-up was on April 22, 2022. The included patients had an acute exacerbation of COPD and a $Paco_2$ level greater than 45 mm Hg after receiving 6 hours of low-intensity NPPV.

INTERVENTIONS Patients were randomized 1:1 to receive high-intensity NPPV with inspiratory positive airway pressure that was adjusted to obtain a tidal volume 10 mL/kg to 15 mL/kg of predicted body weight (n = 147) or to continue receiving low-intensity NPPV with inspiratory positive airway pressure that was adjusted to obtain a tidal volume of 6 mL/kg to 10 mL/kg of predicted body weight (n = 153). Patients in the low-intensity NPPV group who met the prespecified criteria for the need for endotracheal intubation were allowed to crossover to high-intensity NPPV.

MAIN OUTCOMES AND MEASURES The primary outcome was the need for endotracheal intubation during hospitalization, which was defined by prespecified criteria. There were 15 prespecified secondary outcomes, including endotracheal intubation.

RESULTS The trial was terminated by the data and safety monitoring board and the trial steering committee after an interim analysis of the first 300 patients. Among the 300 patients who completed the trial (mean age, 73 years [SD, 10 years]; 68% were men), all were included in the analysis. The primary outcome of meeting prespecified criteria for the need for endotracheal intubation occurred in 7 of 147 patients (4.8%) in the high-intensity NPPV group vs 21 of 153 (13.7%) in the low-intensity NPPV group (absolute difference, −9.0% [95% CI, −15.4% to −2.5%], 1-sided $P = .004$). However, rates of endotracheal intubation did not significantly differ between groups (3.4% [5/147] in the high-intensity NPPV group vs 3.9% [6/153] in the low-intensity NPPV group; absolute difference, −0.5% [95% CI, −4.8% to 3.7%], $P = .81$). Abdominal distension occurred more frequently in the high-intensity NPPV group (37.4% [55/147]) compared with the low-intensity NPPV group (25.5% [39/153]).

CONCLUSIONS AND RELEVANCE Patients with COPD and persistent hypercapnia in the high-intensity NPPV group (vs patients in the low-intensity NPPV group) were significantly less likely to meet criteria for the need for endotracheal intubation; however, patients in the low-intensity NPPV group were allowed to crossover to high-intensity NPPV, and the between-group rate of endotracheal intubation was not significantly different.

Visual Abstract
Editorial
Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

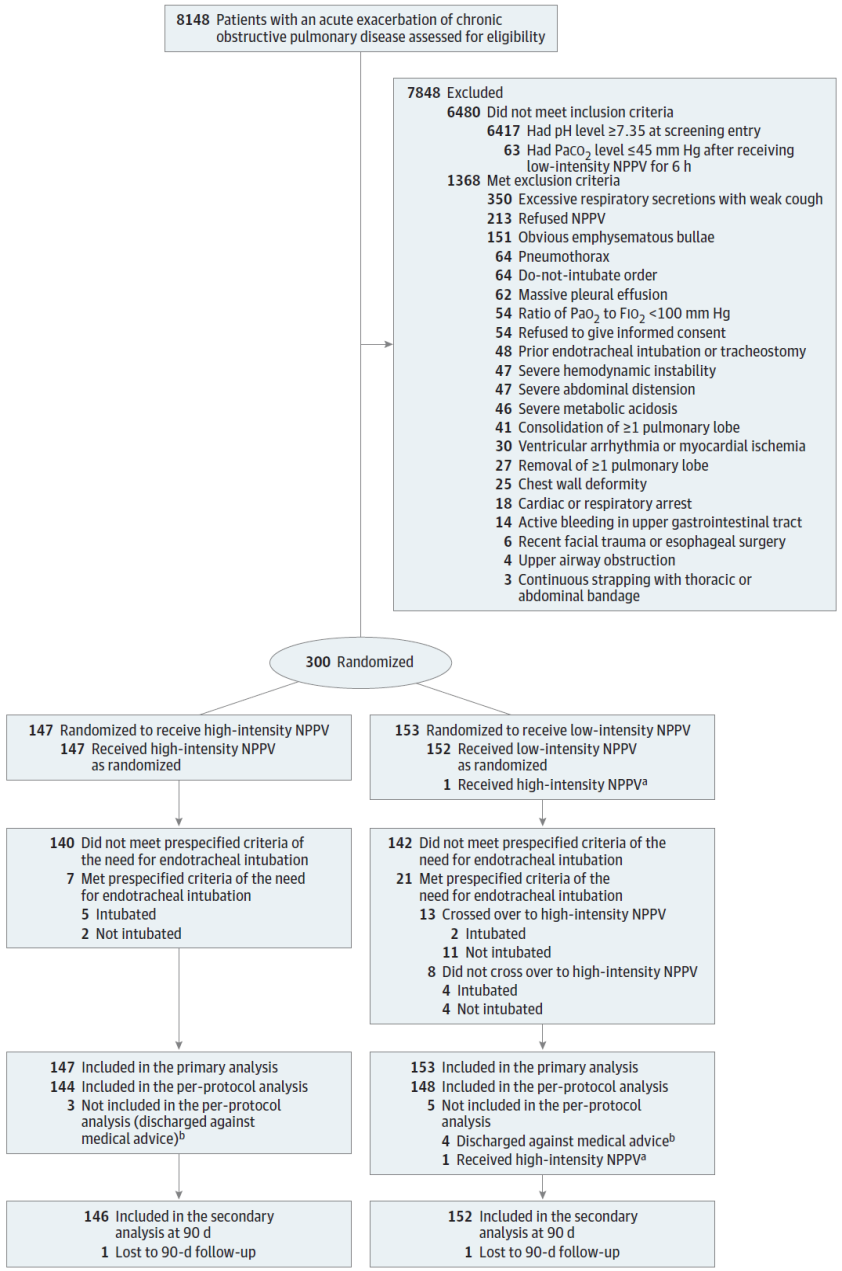
Group Information: A list of the HAPPEN Investigators appears in Supplement 4.

HAPPEN randomized clinical trial

- P : 300 patients with AECOPD and hypercapnia (pCO_2 > 45mmHg) after receiving 6hrs of low-intensity NPPV
- I : High-intensity NPPV (tidal volume 10-15mL/kg, IPAP 20-30)
- C : Low-intensity NPPV (tidal volume 6-10mL/kg, IPAP up to 20)
- O : The need for endotracheal intubation during hospitalization

JAMA. 2024 Sep 16:e2415815

Nonpharmacological management of ECOPD



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Nonpharmacological management of ECOPD

	Noninvasive positive pressure ventilation (NPPV)	
	High intensity (n = 147)	Low intensity (n = 153)
Age, mean (SD), y	73 (9)	73 (10)
Sex, No. (%)		
Male	100 (68)	103 (67)
Female	47 (32)	50 (33)
Height, mean (SD), cm	165 (8)	164 (8)
Body weight, mean (SD), kg		
Actual	65 (13)	64 (14)
Predicted[a]	60 (9)	59 (9)
Body mass index, mean (SD)[b]	24 (5)	24 (5)
COPD-related characteristics[c]		
Smoking history		
Ever smoked, No. (%)	90 (61)	98 (64)
Currently smoke, No. (%)	48 (33)	63 (41)
Median (IQR) [total], pack-years	40 (20-60) [n = 90]	30 (20-50) [n = 98]
Pulmonary function[d]		
FEV_1, mean (SD) [total], % predicted	35 (12) [n = 116]	38 (12) [n = 127]
Ratio of FEV_1 to FVC, mean (SD) [total]	47 (12) [n = 116]	48 (11) [n = 127]
Measured within previous 1 y, No. (%)	47 (32)	52 (34)
Measured at hospital discharge, No. (%)	69 (47)	75 (49)
Disease course, median (IQR), y	15 (10-20)	10 (9-30)
Treatment use, No. (%)		
Long-acting inhaled bronchodilators	124 (84)	133 (87)
Inhaled corticosteroids	116 (79)	122 (80)
Long-term oxygen therapy[e]	85 (58)	98 (64)
Long-term home NPPV[f]	28 (19)	32 (21)
Previous NPPV	81 (55)	89 (58)
Comorbidities, No. (%)[c]		
Chronic heart failure	73 (50)	70 (46)
Hypertensive heart disease	65 (44)	71 (46)
Ischemic heart disease	44 (30)	44 (29)
Diabetes	21 (14)	25 (16)
Obstructive sleep apnea	16 (11)	12 (8)
Atrial fibrillation	15 (10)	10 (7)
Cerebrovascular disease	10 (7)	14 (9)
Chronic kidney failure	6 (4)	3 (2)
Prior myocardial infarction	4 (3)	1 (1)
Peripheral vascular disease	2 (1)	3 (2)
Prior percutaneous coronary intervention	2 (1)	1 (1)
Exacerbation-related characteristics, No. (%)		
Respiratory infection	103 (70)	100 (65)
Pneumonia	31 (21)	38 (25)
Heart failure	50 (34)	46 (30)
Exposure to air pollutants	3 (2)	4 (3)
Undetermined	10 (7)	13 (9)
Time from exacerbation to randomization, median (IQR), d[g]	6 (3-10)	6 (3-10)
Arterial blood gas levels at randomization, mean (SD)[h]		
pH	7.31 (0.06)	7.31 (0.05)
$Paco_2$, mm Hg	79 (15)	79 (15)
Pao_2:Fio_2, mm Hg	206 (59)	200 (51)
Bicarbonate, mmol/L	38 (7)	39 (7)

	Noninvasive positive pressure ventilation (NPPV)	
	High intensity (n = 147)	Low intensity (n = 153)
Disease status score, mean (SD)		
Modified Medical Research Council dyspnea scale[i,j]	3 (1)	3 (1)
COPD Assessment Test[j,k]	25 (6)	26 (7)
Acute Physiology and Chronic Health Evaluation II[l]	17 (4)	17 (4)

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Nonpharmacological management of ECOPD

	Noninvasive positive pressure ventilation (NPPV)				Ratio measure (95% CI)[b]	
	High intensity (n = 147)	Low intensity (n = 153)	Unadjusted absolute difference (95% CI)[a]	*P* value	Unadjusted	Adjusted[c]
Primary outcome[d]						
Need for endotracheal intubation during hospitalization, No. (%)	7 (4.8)	21 (13.7)	−9.0 (−15.4 to −2.5)	.004[e]	0.35 (0.14 to 0.76)	0.30 (0.11 to 0.69)
Secondary outcomes[d]						
Endotracheal intubation during hospitalization, No. (%)	5 (3.4)	6 (3.9)	−0.5 (−4.8 to 3.7)	.81	0.87 (0.25 to 2.72)	0.88 (0.24 to 2.97)
Endotracheal intubation at 28 d, No. (%)						
Met prespecified criteria for the need for intubation	7 (4.8)	21 (13.7)	−9.0 (−15.4 to −2.5)	.008	0.35 (0.14 to 0.76)	0.30 (0.11 to 0.69)
Intubated	5 (3.4)	6 (3.9)	−0.5 (−4.8 to 3.7)	.81	0.87 (0.25 to 2.72)	0.88 (0.24 to 2.97)
Composite of endotracheal intubation or avoiding intubation, No. (%)[f]	5 (3.4)	17 (11.1)	−7.7 (−13.5 to −1.9)	.01	0.31 (0.10 to 0.76)	0.27 (0.08 to 0.69)
NPPV weaning success, No. (%)	97 (66.0)	104 (68.0)	−2.0 (−12.6 to 8.7)	.71	0.97 (0.80 to 1.12)	0.98 (0.81 to 1.13)
Mortality, No./total (%)						
During hospitalization	1/147 (1.0)	4/153 (2.6)	−1.9 (−6.0 to 1.4)[g]	.37[h]	0.26 (0.01 to 1.72)	0.25 (0.01 to 1.78)
At 28 d	2/147 (1.4)	3/153 (2.0)	−0.6 (−4.5 to 3.2)[g]	>.99[h]	0.69 (0.09 to 3.97)	0.81 (0.10 to 5.37)
At 90 d	6/146 (4.1)	6/152 (4.0)	0.2 (−4.3 to 4.6)	.94	1.04 (0.33 to 3.11)	1.00 (0.31 to 3.07)
ICU admission, No. (%)	4 (2.7)	5 (3.3)	−0.6 (−5.2 to 4.0)[g]	>.99[h]	0.83 (0.21 to 2.98)	0.81 (0.19 to 3.01)
Discharged alive from the hospital, No. (%)	143 (97.3)	144 (94.1)	3.2 (−1.4 to 7.7)	.18	1.03 (0.98 to 1.05)	1.03 (0.97 to 1.05)
Length of hospital stay, median (IQR), d						
Overall	10 (8 to 13)	10 (9 to 15)	0 (−1 to 1)[i]	.22	HR, 1.10 (0.88 to 1.38)	HR, 1.10 (0.88 to 1.38)
After randomization	9 (7 to 13)	10 (8 to 14)	−1 (−2 to 1)[i]	.09	HR, 1.08 (0.86 to 1.35)	HR, 1.08 (0.86 to 1.36)
Invasive ventilator-free days at 28 d, median (IQR), d	28 (28 to 28)	28 (28 to 28)	0	.79	NA[j]	NA[j]
ICU-free days at 28 d, median (IQR), d	28 (28 to 28)	28 (28 to 28)	0	.77	NA[j]	NA[j]
Hospital readmission at 90 d, No./total (%)	21/146 (14.4)	22/152 (14.5)	−0.1 (−8.1 to 7.9)	.98	0.99 (0.56 to 1.68)	0.93 (0.52 to 1.60)

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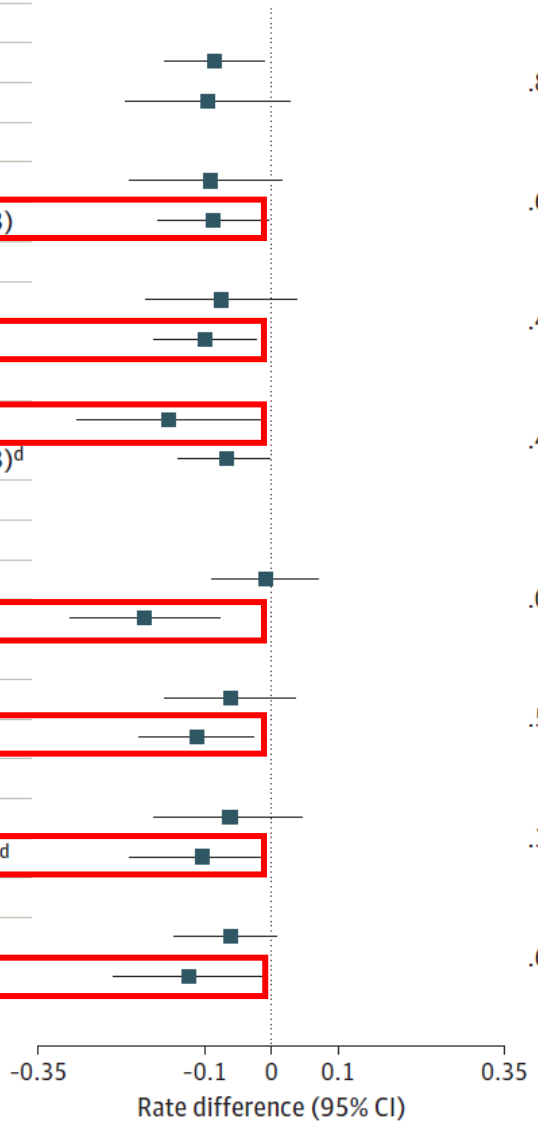
Nonpharmacological management of ECOPD

Subgroup[a]	No./total (%) of patients: High-intensity NPPV	No./total (%) of patients: Low-intensity NPPV	Rate difference (95% CI)[b]	*P* value for interaction[c]
Prespecified				
Sex				
Male	4/100 (4)	13/103 (13)	-0.09 (-0.16 to -0.01)	.84
Female	3/47 (6)	8/50 (16)	-0.10 (-0.22 to 0.03)	
Age group, y				
<70	2/57 (4)	7/55 (13)	-0.09 (-0.21 to 0.02)[d]	.67
≥70	5/90 (6)	14/98 (14)	-0.09 (-0.17 to -0.003)	
Ever smoked				
No	4/57 (7)	8/55 (15)	-0.08 (-0.19 to 0.04)	.49
Yes	3/90 (3)	13/98 (13)	-0.10 (-0.18 to -0.02)	
pH level at randomization[e]				
<7.3	6/63 (10)	13/52 (25)	-0.15 (-0.29 to -0.02)	.47
≥7.3	1/84 (1)	8/101 (8)	-0.07 (-0.14 to -0.003)[d]	
Post hoc				
Level of $PaCO_2$ at randomization, mm Hg[e]				
<80	4/80 (5)	5/85 (6)	-0.01 (-0.09 to 0.07)[d]	.06
≥80	3/67 (4)	16/68 (24)	-0.19 (-0.30 to -0.08)	
Ratio of PaO_2 to FIO_2 at randomization, mm Hg[e]				
<200	5/66 (8)	11/80 (14)	-0.06 (-0.16 to 0.04)	.58
≥200	2/81 (2)	10/73 (14)	-0.11 (-0.20 to -0.03)	
FEV_1, % predicted				
<35	3/57 (5)	7/61 (11)	-0.06 (-0.18 to 0.05)[d]	.35
≥35	1/59 (2)	8/66 (12)	-0.10 (-0.21 to -0.01)[d]	
APACHE II score				
<17	1/76 (1)	6/81 (7)	-0.06 (-0.15 to 0.01)[d]	.61
≥17	6/71 (8)	15/72 (21)	-0.12 (-0.24 to -0.01)	



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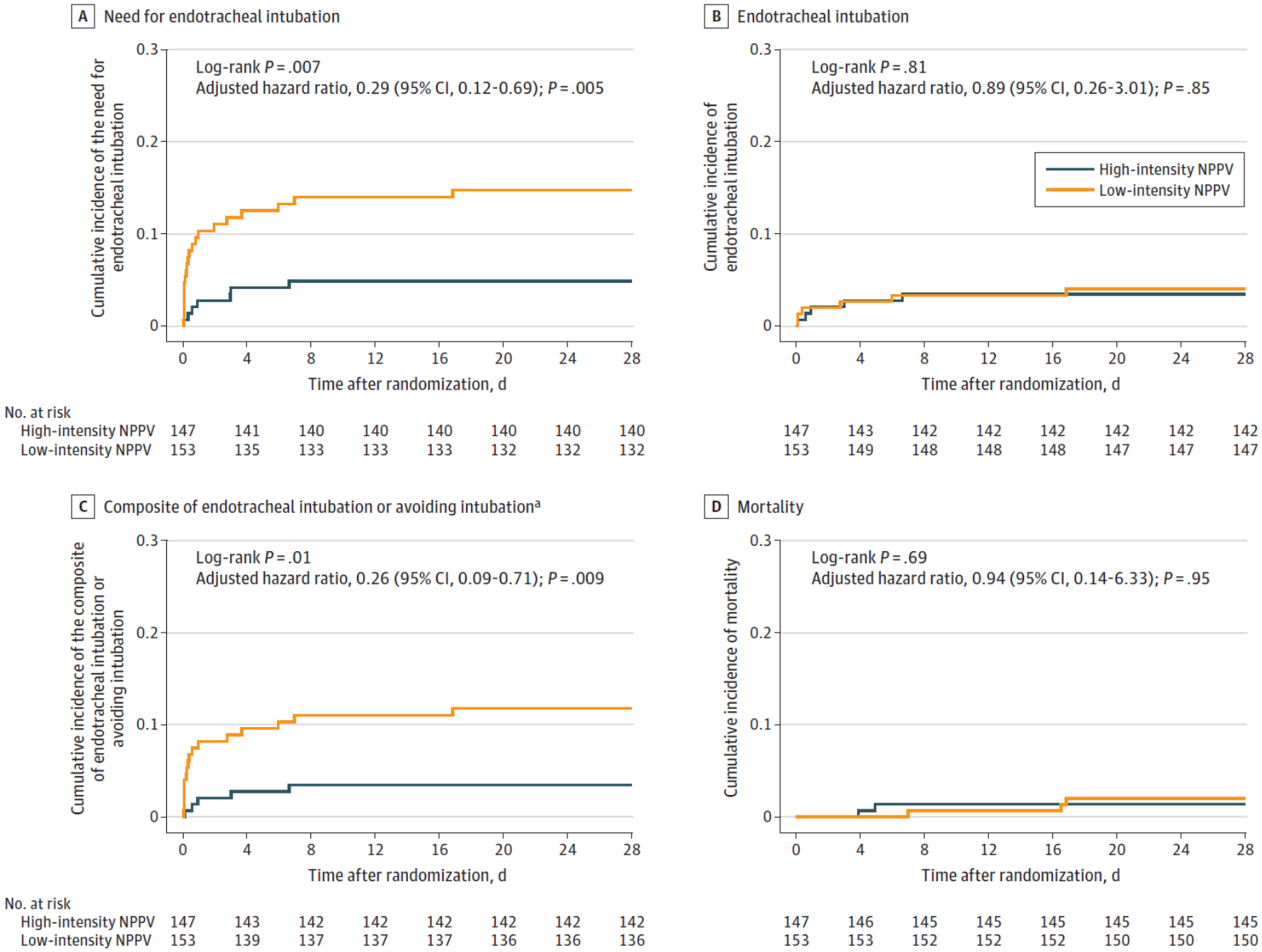
Nonpharmacological management of ECOPD

Figure 3. Kaplan-Meier Curves for 4 Outcomes in the Noninvasive Positive Pressure Ventilation (NPPV) Groups



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Nonpharmacological management of ECOPD

Table 3. Safety Outcomes and Serious Adverse Events

	Noninvasive positive pressure ventilation (NPPV), No. (%)	
	High intensity (n = 147)	Low intensity (n = 153)
Safety outcomes[a]		
Complications related to NPPV		
Abdominal distension	55 (37.4)	39 (25.5)
Nasal or oral dryness	44 (29.9)	46 (30.1)
Severe air leakage[b]	26 (17.7)	17 (11.1)
Severe intolerance to NPPV[c]	11 (7.5)	6 (3.9)
Inability to remove respiratory secretions	8 (5.4)	9 (5.9)
Nasal or facial skin necrosis	3 (2.0)	6 (3.9)
Claustrophobia	3 (2.1)	4 (2.6)
Intolerance to NPPV because of abdominal distension	5 (3.4)	1 (0.7)
Aspiration	1 (0.7)	1 (0.7)
Hypotension	2 (1.4)	0
Conjunctivitis	0	1 (0.7)
Serious adverse events		
Severe alkalosis	6 (4.1)	0
Gastrointestinal tract bleeding	0	3 (2.0)
Nosocomial pneumonia	0	2 (1.3)
Septic shock	1 (0.7)	1 (0.7)
Multiple organ failure	1 (0.7)	1 (0.7)
Cardiac arrest	0	2 (1.3)

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Original Research

Nasal high flow or noninvasive ventilation? navigating hypercapnic COPD exacerbation treatment: A randomized noninferiority clinical trial

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ARTICLE INFO

Keywords:
Nasal high flow
Noninvasive ventilation
Hypercapnia
COPD
Respiratory failure type II

ABSTRACT

Background: Noninvasive ventilation (NIV) has been the cornerstone for managing acute exacerbations of COPD (AECOPD) with hypercapnic respiratory failure. Nasal high flow (NHF) oxygen therapy has emerged as a potential alternative, offering a more tolerable modality with promising outcomes. The aim of the present study was to evaluate whether NHF respiratory support is noninferior to NIV with respect to treatment failure, in patients with mild-to-moderate hypercapnic AECOPD.

Methods: In this multi-center, randomized, noninferiority trial, 105 patients with AECOPD and respiratory failure type II were enrolled. Participants were randomly assigned to receive either NHF therapy or NIV. The primary endpoint was the frequency of treatment failure, defined as the need for intubation and invasive mechanical ventilation or a switch to the alternative treatment group. Secondary endpoints included changes in respiratory parameters, patient comfort indicators, and the occurrence of complications.

Results: The findings revealed no significant difference in the primary outcome between the groups, with a treatment failure rate of 19.6 % (10 out of 51) in the NHF group and 14.8 % (8 out of 54) in the NIV group. Interestingly, NHF users reported significantly lower levels of dyspnea and discomfort at multiple follow-up points. Despite the differences in patient comfort, respiratory parameters such as respiratory rate, arterial blood gases, and use of accessory muscles of respiration showed no significant disparities between the groups throughout the study period.

Conclusions: NHF therapy was similar to NIV in preventing treatment failure among patients with hypercapnic AECOPD, offering a viable alternative with enhanced comfort.

Trial registration: The study was prospectively registered in ClinicalTrials.gov (Identifier: NCT03466385) on March 15, 2018.

NIV vs NHF

- P : 105 patients with AECOPD and type 2 respiratory failure
- I : NHF
- C : NIV
- O : frequency of treatment failure, defined as the need for intubation and invasive mechanical ventilation or a switch to the alternative treatment group

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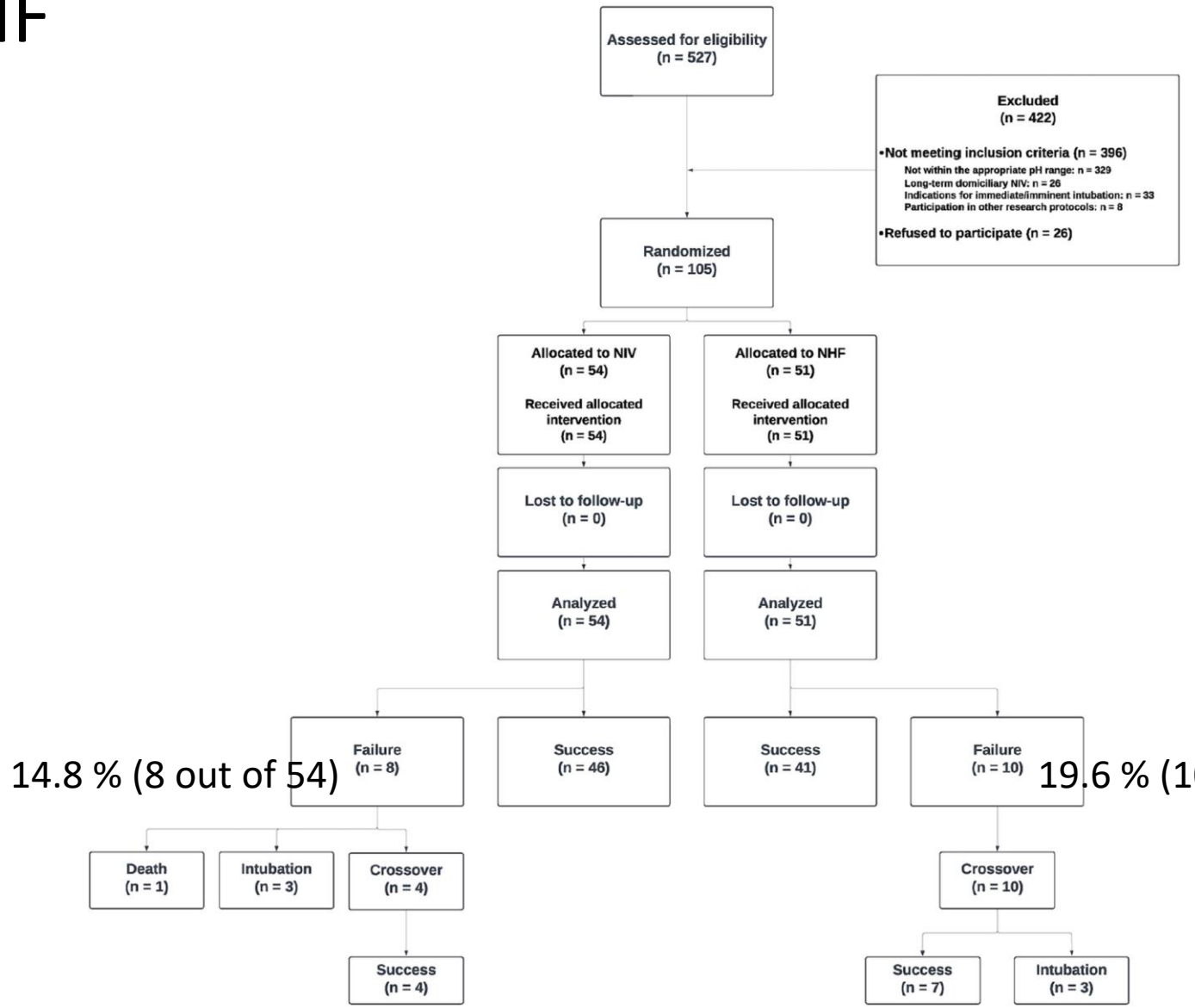
NIV vs NHF



14.8 % (8 out of 54)

19.6 % (10 out of 51)

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NIV vs NHF ; baseline characteristics

Baseline parameters for both study groups.

Parameter	Group		p value
	NIV (n = 54)	NHF (n = 51)	
Age (years)	73.26 ± 9.50	72.37 ± 9.18	0.63
Charlson Comorbidity Index	5 (1.25)	5 (2)	0.07
BMI (kg/m^2)	25.54 (5.19)	24.98 (5.06)	0.23
SAP (mmHg)	130 (15)	135 (20)	0.17
DAP (mmHg)	77.50 (20.25)	75 (12)	0.14
HR (bpm)	105 (15)	105 (15)	0.50
RR (breaths/min)	32.50 (10)	30 (6)	0.56
Borg scale	8 (1.25)	7 (3)	0.62
VAS scale	8 (2)	7 (2)	0.09
PaO_2/FiO_2	238.10 (43.19)	237.78 (58.27)	0.28
pH	7.29 (0.05)	7.30 (0.03)	0.41
pCO_2 (mmHg)	65 (13)	60.80 (10)	0.07
HCO_3(mEq/L)	30.45 (5.70)	30.10 (4.30)	0.47
SaO2 (mmHg)	85.64 ± 6.52	85.82 ± 6.20	0.88
Male gender	41 (75.93 %)	34 (66.67 %)	0.39
Accessory muscles use	45 (83.33 %)	48 (94.12 %)	0.12
Smoking status			
Current	35 (64.81 %)	32 (62.75 %)	0.84
Former	19 (35.19 %)	19 (37.25 %)	

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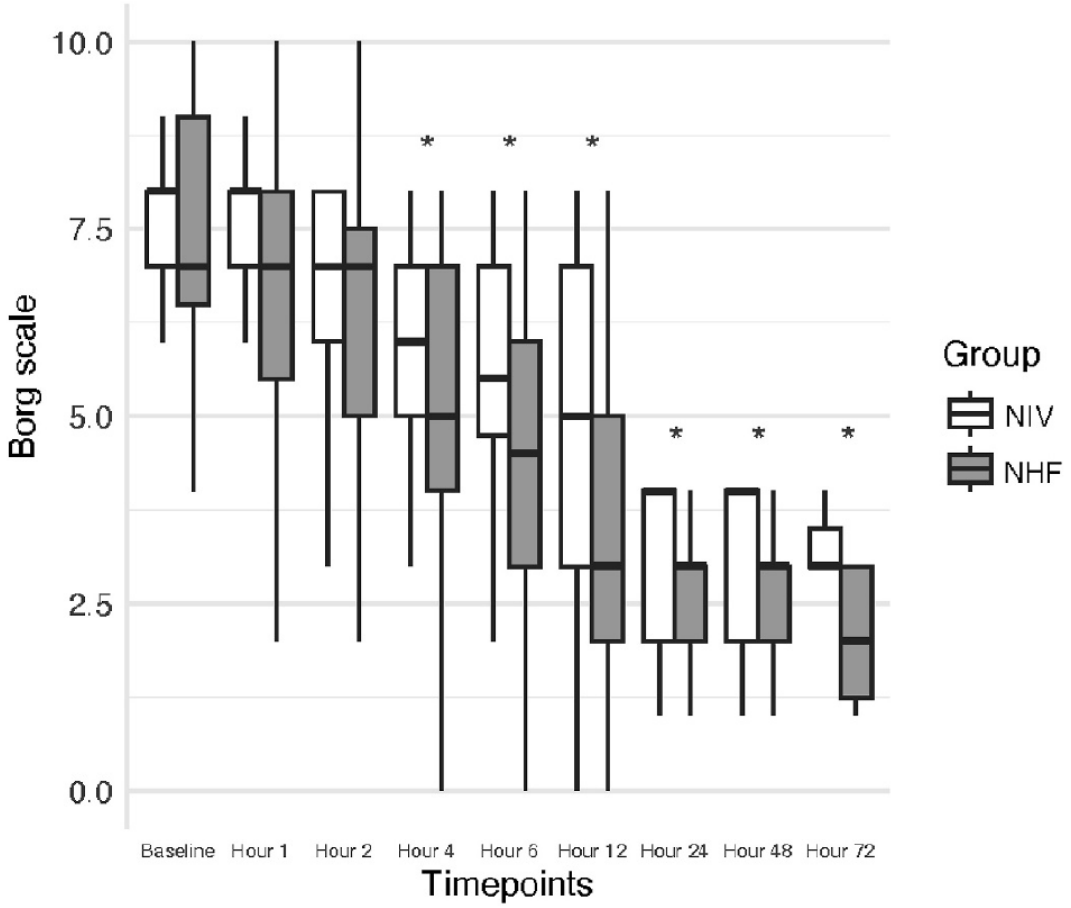
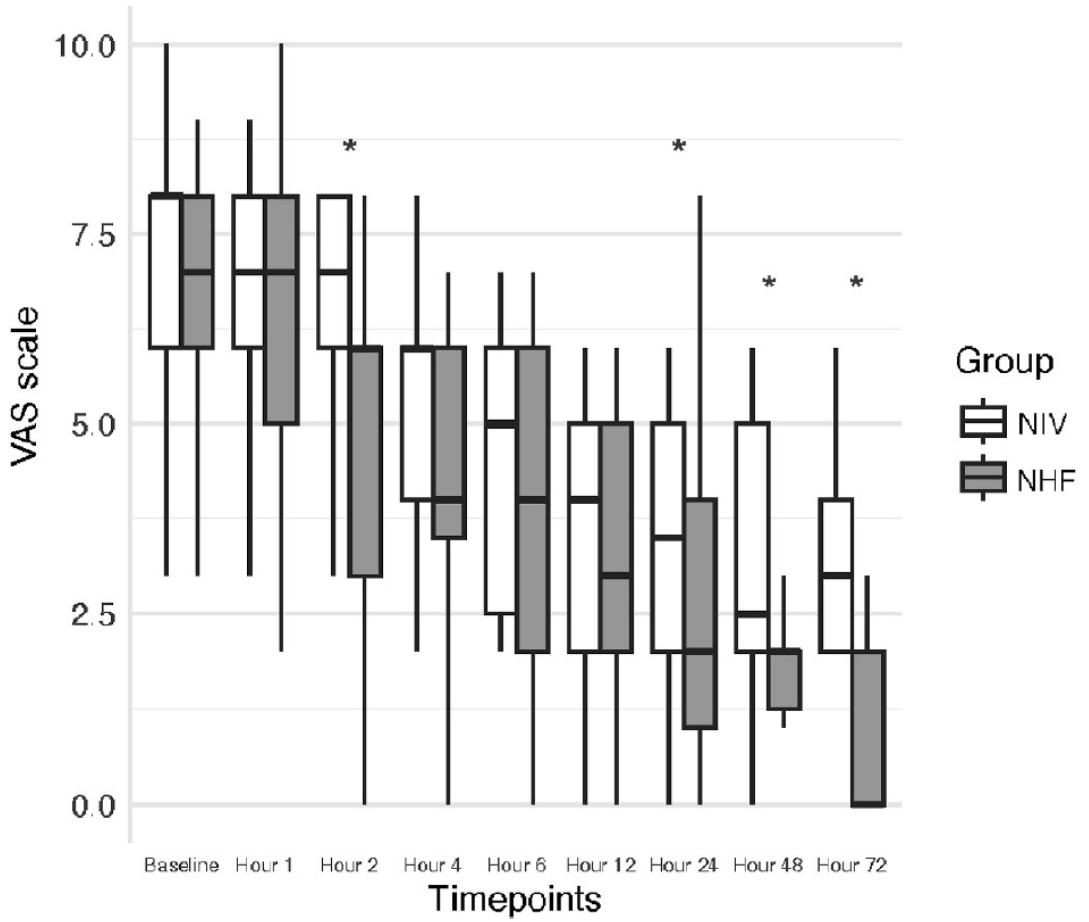
NIV vs NHF ; dyspnea and discomfort parameters





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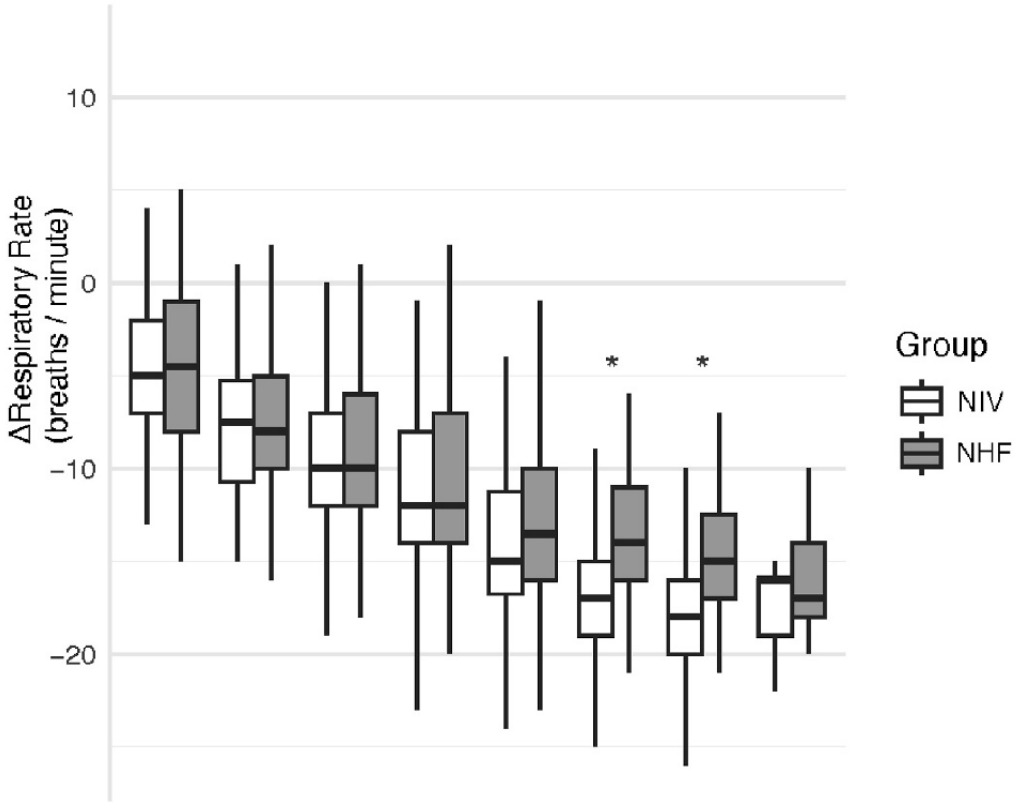
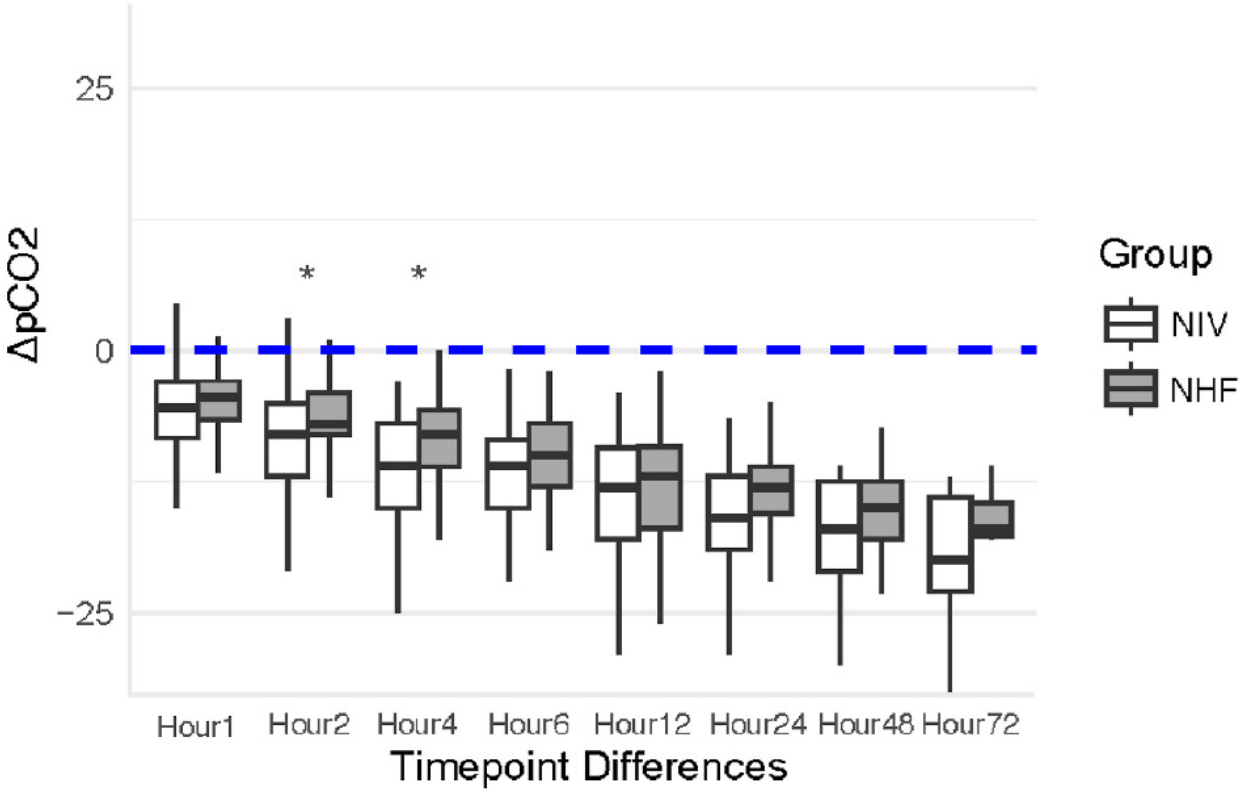
NIV vs NHF ; respiratory parameters





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Nonpharmacological management of ECOPD

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Routine in-hospital interventions during acute exacerbation of COPD are associated with improved 30-day care

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ARTICLE INFO

Keywords:
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Hospitalization
Patient care
In-hospital interventions
Therapy

ABSTRACT

Background: Implementing standard of care therapy for chronic obstructive pulmonary disease (COPD) has barriers. Hospitalization with an acute exacerbation of COPD (AECOPD) is a major adverse event that could also be an opportunity to improve patients' long-term care.
Objectives: To evaluate which in-hospital interventions during AECOPD are associated with improved 30-day care.
Methods: This was a prospective study that included patients from 10 medical centers across Israel, hospitalized with AECOPD between 2017 and 2019. Patients were approached during hospitalization in internal medicine departments. A semi-structured follow-up call was performed 30 days after discharge, and six COPD areas of care were assessed. Multivariate analyses were used to analyze predictors for each area of care.
Results: 234 patients were included (mean age 69 years and 34% females). A lower 30-day readmission rate was independently associated with smoking cessation and prescription of renin-angiotensin blockers. Initiating or continuing long acting bronchodilators (LABD) during admission was an independent predictor for their 30-day use. Among patients with prior LABD treatment, only 38% continued at 30-days if it was not prescribed during admission (OR 4, 95% CI 1.98-8.08, $p<0.01$). In-hospital daily respiratory physiotherapy was an independent predictor for smoking cessation (AOR 5.1, 95% CI 1.1-23, $p=0.04$), while smoking cessation recommendation was not ($p=0.28$). Initiating a smoking cessation program (5%) or pulmonary rehabilitation (1%) after discharge was performed only by patients with a written referral.
Conclusion: Routine procedures during hospitalization for AECOPD could impact patients' long-term care in areas with proven effects on disease outcomes.

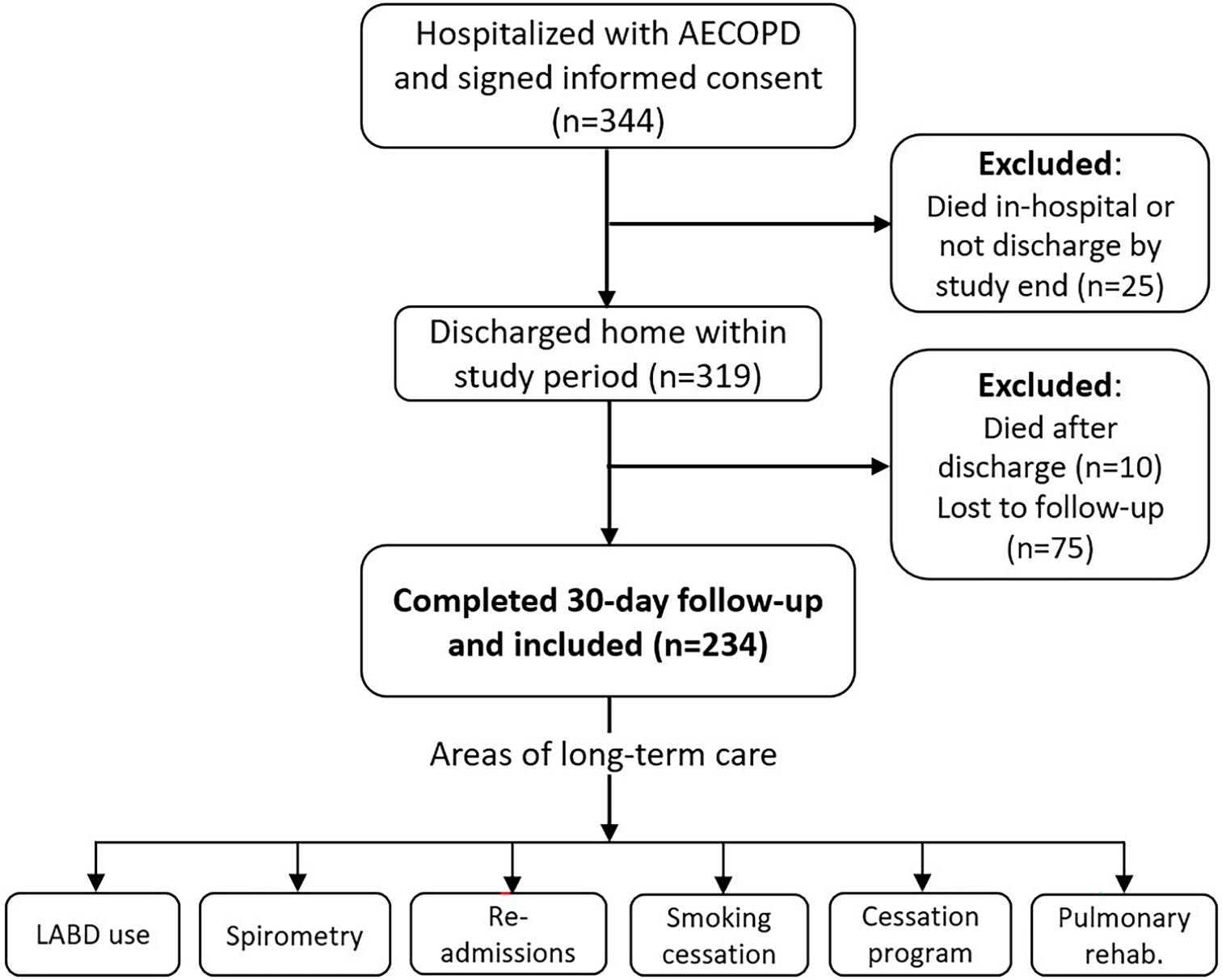
Heart Lung. 2024 Sep-Oct:67:114-120

In-hospital interventions during AECOPD

- Prospective multicenter cohort study, COPD Israeli survey (COPDIS)
- Analyzed in-hospital interventions affecting re-admission

Heart Lung. 2024 Sep-Oct:67:114-120

Nonpharmacological management of ECOPD



Heart Lung. 2024 Sep-Oct:67:114-120

Nonpharmacological management of ECOPD

Table 1
Baseline characteristics of the study cohort and in-hospital interventions.

Variable	Total, n=234 (%)
Age	69 ± 11
Female sex	80 (34)
Obese (BMI>30)	82 (35)
Dyslipidemia	103 (44)
Hypertension	136 (58)
Diabetes	87 (37)
Smoking (prior/current)	225 (92)
Ischemic heart disease	59 (25)
Heart failure	50 (21)
Pulmonologist visit in last 5 years	189 (81)
Prior COPD exacerbation	160 (68)
MMRC score above 1	160 (68)
Prior pulmonary rehabilitation	
In past 12 months	15 (6)
More than 12 months ago	21 (9)
Use home oxygen	90 (38)
In-hospital interventions:	
LABD treatment	77 (33)
SABD treatment	220 (94)
Non-invasive ventilation	70 (30)
Respiratory physiotherapy	49 (21)
Oxygen-requirement at discharge	144 (62)
Discharge prescriptions:	
Inhaled corticosteroids	152 (65)
LABD	133 (57)
SABD	191 (82)
ACEi / ARB	89 (38)
Antiplatelet therapy	98 (42)
Statins	102 (44)
Discharge plan:	
Referral to pulmonologist	182 (78)
Referral to spirometry	39 (17)
Referral to rehabilitation	29 (12)
Smoking cessation recommendation	43 (41)
Referral to smoking cessation program	12 (12)

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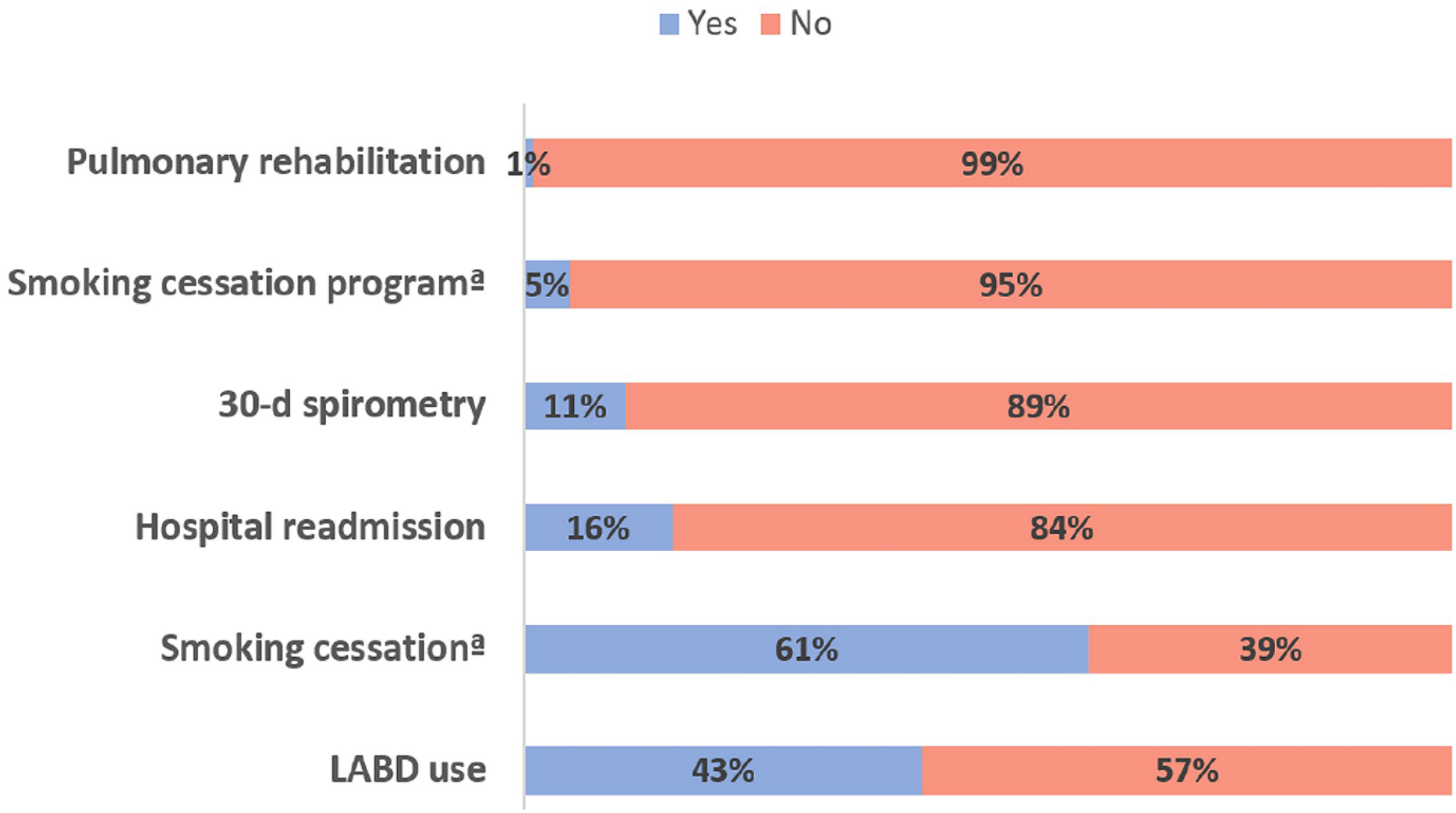
Nonpharmacological management of ECOPD

Table 2
Predictors for 30-day hospital readmission.

Variable	Univariate		Multivariate	
	OR (95% CI)	*p*	AOR (95% CI)	*p*
Prior COPD exacerbation	6.63 (2.0-22)	<0.01	4.36 (1.2-15)	**0.02**
MMRC score above 1	4.72 (1.6-14)	<0.01	1.93 (0.8-4.6)	0.14
Heart failure history	2.24 (1.1-4.8)	0.04	1.49 (0.6-3.4)	0.35
Living near a main roadway	3.37 (1.6-7.3)	<0.01	2.33 (1.1-5.3)	**0.04**
Continue smoking after discharge[a]	8.28 (2.2-32)	<0.01	9.73 (1.9-41)	**0.01**
Discharge prescriptions:				
ACEi / ARB	0.42 (0.2-0.9)	0.02	0.43 (0.2-0.97)	**0.04**
LABD	1.26 (0.6-2.6)	0.54	–	–
Anti-platelets	0.96 (0.5-1.9)	0.91	–	–
Statins	0.89 (0.4-1.8)	0.73	–	–
Discharge plan:				
Referral to pulmonologist	0.94 (0.4-2.1)	0.89	–	–
Smoking cessation recommendation	1.31 (0.4-3.9)	0.63	–	–
Referral to spirometry	0.52 (0.2-1.6)	0.24	–	–

Heart Lung 2024 Sep-Oct:67:114-120

Nonpharmacological management of ECOPD



Heart Lung 2024 Sep-Oct:67:114-120

Nonpharmacological management of ECOPD

Table 3
Predictors for long-acting bronchodilators use at 30-days.

Variable	Univariate		Multivariate	
	OR (95% CI)	*p*	AOR (95% CI)	*p*
Pulmonologist visit in 5 years	2.10 (1.1-4.3)	0.04	1.99 (0.4-9.2)	0.42
MMRC score above 1	3.61 (1.9-6.7)	<0.01	1.75 (0.8-3.8)	0.16
Prior COPD exacerbation	2.97 (1.6-5.4)	<0.01	1.53 (0.7-3.4)	0.31
In-hospital LABD	3.85 (2.0-7.4)	<0.01	2.17 (1.2-4.5)	0.03
Referral to pulmonologist at discharge	1.93 (1.0-3.7)	0.05	1.71 (0.8-3.8)	0.19
Prescribing LABD at discharge	14.5 (7.2-28)	<0.01	7.91 (3.9-18)	<0.01

Table 4
Predictors for smoking cessation at 30-days[a].

Variable	Univariate		Multivariate	
	OR (95% CI)	*p*	AOR (95% CI)	*p*
Older age	1.03 (0.99-1.1)	0.07	1.03 (1.0-1.1)	0.13
Heart failure	3.07 (1.01-9.2)	0.04	1.93 (0.9-3.6)	0.09
Oxygen requirement at discharge	2.87 (1.2-6.7)	0.01	3.21 (1.3-7.8)	0.01
In-hospital respiratory physiotherapy	5.57 (1.2-25)	0.01	5.09 (1.1-23)	0.04
Referral to pulmonologist at discharge	0.49 (0.2-1.5)	0.19		
Smoking cessation recommendation	1.30 (0.6-2.9)	0.28		

[a] Among active smokers at admission (n=104).

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Management of ECOPD ; Year-in-review 2024

- The STARR2 trial demonstrated that BEC-guided steroid administration was non-inferior to routine therapy.
- The results of study of interferon beta nebulizer indicates that this approach may facilitate viral clearance in ECOPD.
- In patients with type 2 respiratory failure and ECOPD, high-intensity NPPV was significantly less likely to result in the need for intubation.
- The results indicated that high flow nasal cannula was comparable to NIV in terms of its efficacy in improving dyspnea in patients with ECPOD and hypercapnia.
- The provision of smoking cessation education to hospitalized ECOPD patients is an effective strategy for the prevention of readmissions.

Prevention of ECOPD

Interventions that Reduce the Frequency of COPD Exacerbations

Figure 4.11

Intervention Class	Intervention
Bronchodilators	LABAs LAMAs LABA + LAMA
Corticosteroid-containing regimens	LABA + ICS LABA + LAMA + ICS
Anti-inflammatory (non-steroid)	Roflumilast Dupilumab
Anti-infectives	Vaccines Long Term Macrolides
Mucoregulators	N-acetylcysteine Carbocysteine Erdosteine
Various others	Smoking Cessation Rehabilitation Lung Volume Reduction Vitamin D Shielding measures (e.g., mask wearing, minimizing social contact, frequent hand washing)

BOREAS trial ; dupilumab for COPD with T2 inflammation

The NEW ENGLAND JOURNAL of MEDICINE

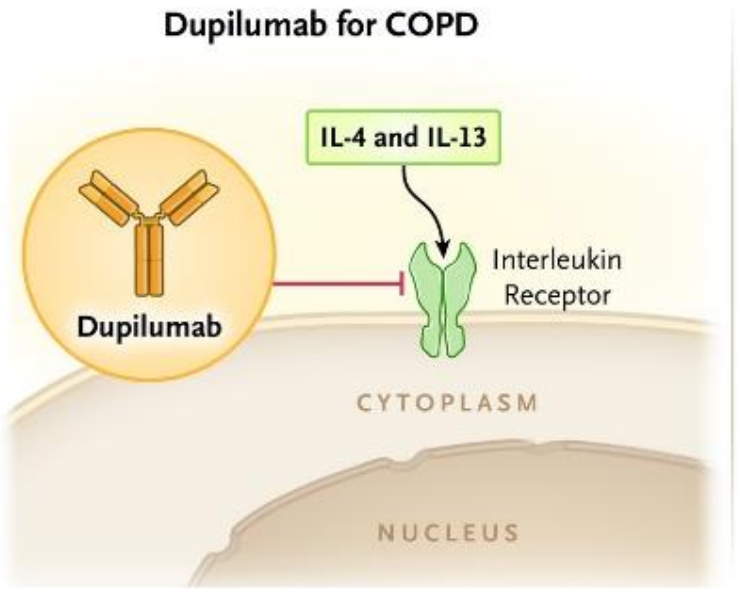
ESTABLISHED IN 1812 JULY 20, 2023 VOL. 389 NO. 3

Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts

S.P. Bhatt, K.F. Rabe, N.A. Hanania, C.F. Vogelmeier, J. Cole, M. Bafadhel, S.A. Christenson, A. Papi, D. Singh, E. Laws, L.P. Mannent, N. Patel, H.W. Staudinger, G.D. Yancopoulos, E.R. Mortensen, B. Akinlade, J. Maloney, X. Lu, D. Bauer, A. Bansal, L.B. Robinson, and R.M. Abdulai, for the BOREAS Investigators*

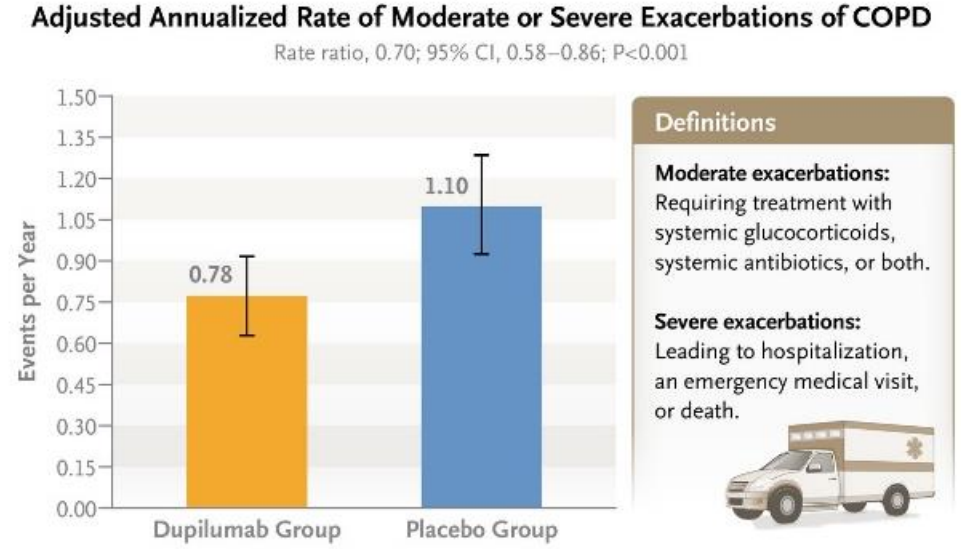
N Engl J Med 2023;389:205-214

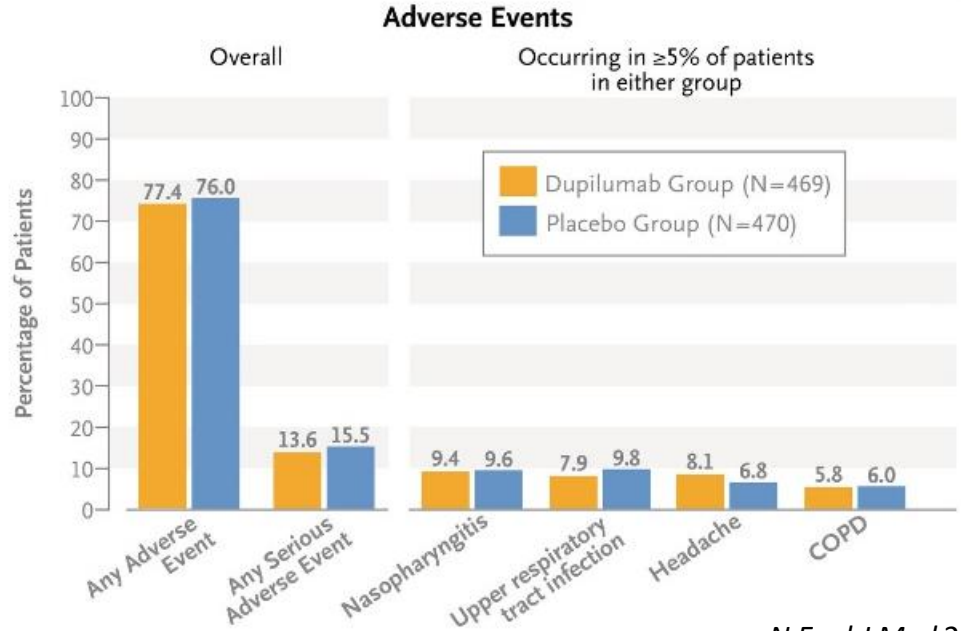
BOREAS trial ; dupilumab for COPD with T2 inflammation



Dupilumab, 300 mg
(N=468)

Placebo
(N=471)





N Engl J Med 2023;389:205-214

RESEARCH/Original Article

Effect of telemonitoring on readmissions for acute exacerbation of chronic obstructive pulmonary disease: A randomized clinical trial

Journal of Telemedicine and Telecare
2024, Vol. 30(9) 1417–1424

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Sage

Frank D Andersen[1], Christian Trolle[1], Asger Roer Pedersen[1], Maria L Køpfli[1], Sanne Børgesen[1], Michael S Jensen[2] and Charlotte Hyldgaard[1]

Abstract

Introduction: Acute exacerbations of chronic obstructive pulmonary disease are associated with high morbidity and mortality. Telemonitoring may reduce the frequency of hospitalization. The aim of this study was to investigate the effect of telemonitoring on hospitalization rates for acute exacerbations of chronic obstructive pulmonary disease.

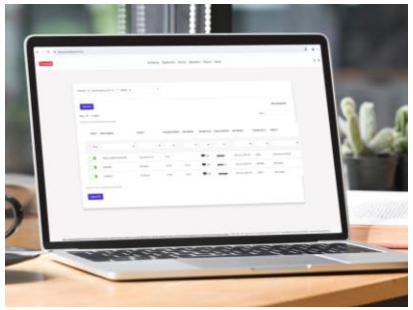
Methods: Patients were recruited during hospitalization and equally randomized to telemonitoring or usual care. Telemonitoring participants recorded symptoms and monitored oxygen saturation, heart rate, peak expiratory flow, and body weight. Alerts were generated if readings breached thresholds. Acute exacerbations of chronic obstructive pulmonary disease hospitalizations during the 6 months intervention were compared using logistic regression, and time to first hospitalization was assessed using Cox proportional hazard modeling. The incidence rates for acute exacerbations of chronic obstructive pulmonary disease hospitalization were compared using a negative binomial regression model with between-group comparisons expressed as incidence rate ratios. The telemonitoring group was used as reference.

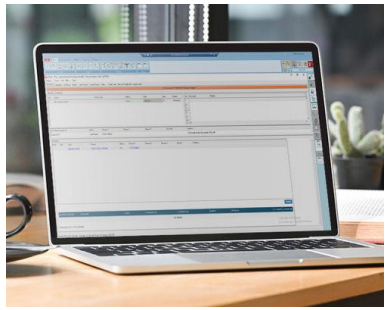
Results: A total of 222 patients were randomized. 37/112 (33%) in the control group and 31/110 (28%) in the telemonitoring group experienced acute exacerbations of chronic obstructive pulmonary disease hospitalization during the intervention period, odds ratio of 1.26, confidence interval 0.71–2.23, $p = 0.4$. No difference was seen in time to first hospitalization, hazard ratio 1.23, CI 0.77–1.99, $p = 0.4$. The number of hospitalizations in the intervention period was 66 in the control group and 42 in the telemonitoring group, with incidence rate ratio 1.42, confidence interval 1.04–1.95, $p = 0.03$. Adjustment for dyspnea score, smoking, and cohabitation status did not change the results, incidence rate ratio 1.44, confidence interval 1.05–1.99, $p = 0.02$.

Discussion: Patients who received telemonitoring experienced significantly fewer acute exacerbations of chronic obstructive pulmonary disease hospitalizations, although the overall risk of having at least one hospitalization and the time to first hospitalization was similar between the two groups.

Telemonitoring of ECOPD patients

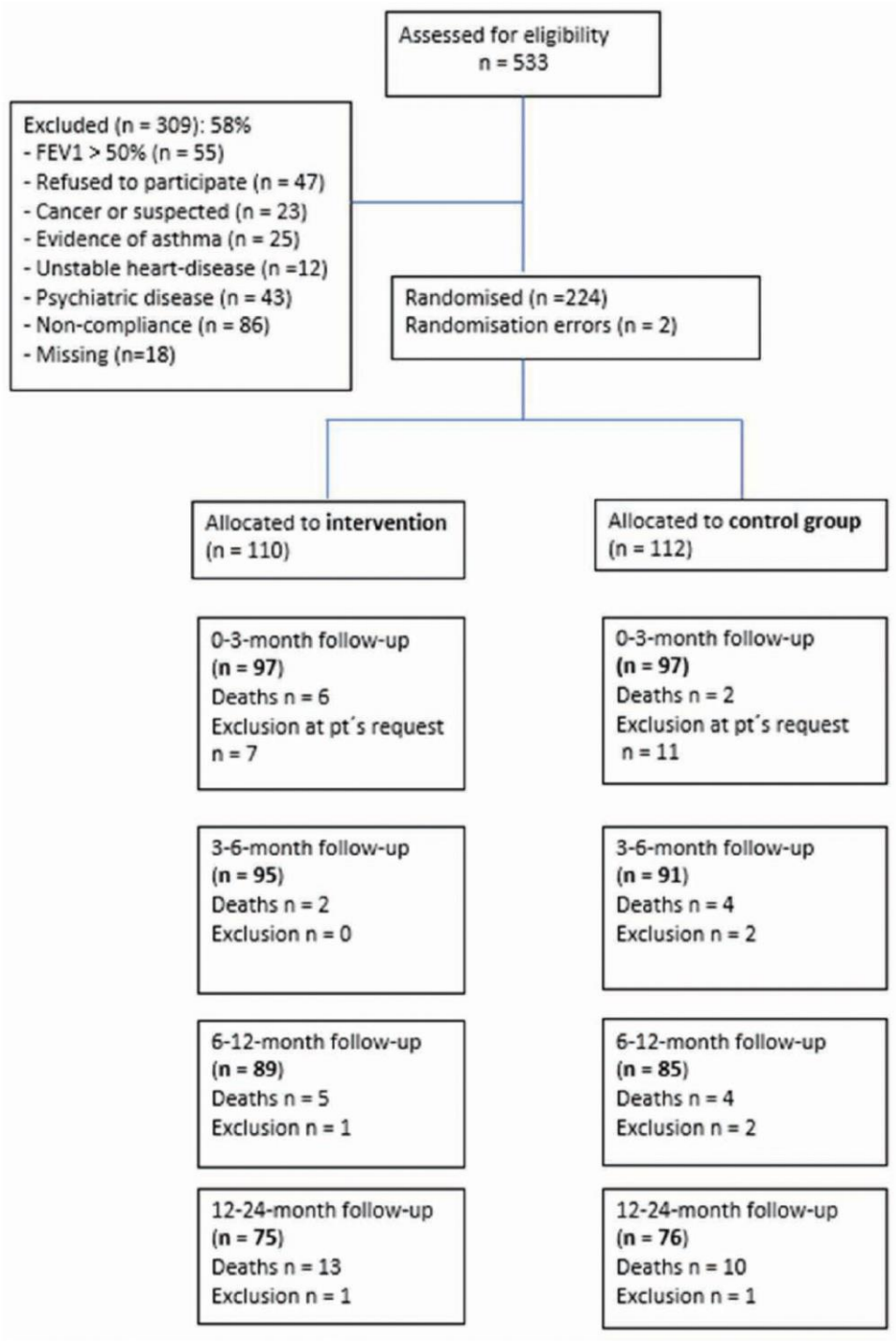
- P : 222 hospitalized patients with ECOPD, FEV1 < 50%
- I : Telemonitoring – home measurement of SpO2, HR, questionnaire of dyspnea, cough, sputum volume
- C :
- O : frequency of treatment failure, defined as the need for intubation and invasive mechanical ventilation or a switch to the alternative treatment group





J Telemed Telecare. 2024 Oct;30(9):1417-1424.

Prevention of ECOPD



J Telemed Telecare. 2024 Oct;30(9):1417-1424.

Table 1. Clinical characteristics for patients in the telemonitoring (TM) and control groups (CGs).

	TM (n = 110)	Control (n = 112)	*P*-value
Age in years, median (IQR)	70 (64–76)	71 (65–76)	*0.3*
Female sex, n (%)	72 (65)	64 (57)	*0.2*
BMI, kg/m^2, median (IQR)	23 (20–27)	22 (19–26)	*0.3*
FEV1% predicted[a], stable state, median (IQR)	34.5 (28–44)	38.0 (19–47)	*0.6*
FEV1% predicted, at time of inclusion, median (IQR)	30.5 (25–37)	30 (24–38)	*0.8*
GOLD classification, stable state	19 (17)	25 (22)	*0.6*
Moderate (FEV1 > 50%)	59 (54)	53 (47)	
Severe (FEV1 30–50%)	32 (29)	34 (30)	
Very severe (FEV1 < 30%)			
Long-term oxygen therapy (LTOT), n (%)	39 (35)	42 (38)	*0.8*
Civil status, n (%)	53 (48)	38 (34)	*0.04*
Living alone	57 (52)	73 (65)	
Married/cohabitating	0	1 (1)	
NA			
Smoking status, n (%)	36 (33)	39 (35)	*1.0*
Current smoker	73 (66)	72 (64)	
Ex-smoker	1 (1)	1 (1)	
Never smoked			
Season for recruitment to the study	32 (29)	28 (25)	*0.9*
Spring, n (%)	23 (21)	26 (23)	
Summer, n (%)	24 (22)	25 (22)	
Autumn, n (%)	31 (28)	33 (29)	
Winter, n (%)			

Prevention of ECOPD

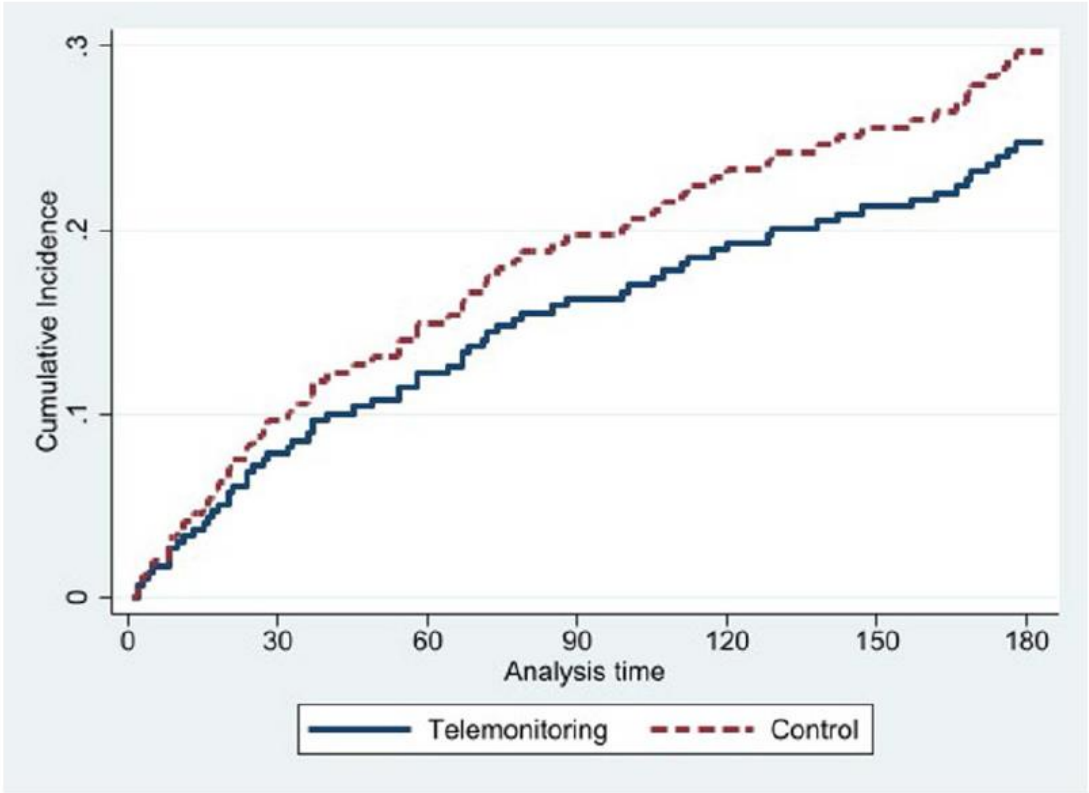
Table 2. Number of hospitalizations and length of stay.

	0–6 months		0–24 months	
	Tele (n = 110)	Control (n = 112)	Tele	Control
Person days in the study	18,101	18,145	65,632	63,872
Deaths	8	6	26	20
Other exits	7	14	9	16
Patients with first readmission	31	37	60	63
Hospitalizations for AECOPD, total	42	66	175	183
Median number of hospitalizations for AECOPD (hospitalized only)	1	2	4	4
Days in hospital for AECOPD	228	392	1066	1171
Median length of stay (hospitalized only)	5	7	4	4
No hospitalizations, n	79	75	50	49
1 hospitalization, n	22	17	19	20
2 hospitalizations, n	7	15	18	16
3 hospitalizations, n	2	2	4	10
4 hospitalizations, n	0	2	6	6
5 hospitalizations, n	0	1	7	6
6 hospitalizations			1	1
7 hospitalizations			3	0
8 hospitalizations			1	2
12 hospitalizations			0	1
13 hospitalizations			0	1
14 hospitalizations			1	0

AECOPD: acute exacerbations of chronic obstructive pulmonary disease.

J Telemed Telecare. 2024 Oct;30(9):1417-1424.

Cumulative incidence estimates for time to first hospitalization during the intervention period



Analysis	IRR	Lower CI	Upper CI	P-value
Hospitalizations, 6 months	1.42	1.04	1.95	0.026
Days in hospital, 6 months	1.22	0.91	1.62	0.176
Hospitalizations, 24 months	1.04	0.89	1.21	0.644
Days in hospital, 24 months	1.08	0.94	1.24	0.285

J Telemed Telecare. 2024 Oct;30(9):1417-1424.

Prevention of ECOPD ; Year-in-review 2024

- FDA has approved dupilumab to be used as an add-on maintenance treatment for adults with inadequately controlled COPD with eosinophilic phenotype, as 1st biologics to be approved for the treatment of COPD patients.
- The findings of the telemonitoring study indicate that the utilization of monitoring device in the management of COPD patients may prove an effective strategy for the reduction of readmission rates.