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Early View

Original research article

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

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Take-home message:

Applying the newly proposed Rome criteria to a real-world cohort of hospitalized COPD patients provides insight in the heterogeneity of exacerbations and shows that these criteria can differentiate between events with different short-term mortality rates.

Abstract

Background: Recently, the Rome classification was proposed in which objective and readily measurable variables were integrated to mark exacerbations of COPD (ECOPD) severity. The aim of this study is to investigate the distribution of a real-world patient population with hospitalized ECOPD according to the current classification across the newly proposed severity classification. We assume that a significant proportion of hospitalized patients will have a mild or moderate event.
Methods: The Rome classification was applied to a cohort of 364 COPD patients hospitalized at the Department of Respiratory Medicine of Maastricht University Medical Center (MUMC) with a severe ECOPD. Differences in in-hospital, 30- and 90-days mortality were compared between mild, moderate and severe ECOPD according to the new classification. Moreover, data was stratified by the different severity classes and compared regarding general disease characteristics and clinical parameters.
Results: According to the Rome proposal, 52 (14.3%) patients had a mild ECOPD, 204 (56.0%) moderate and 108 (29.7%) patients a severe ECOPD. In-hospital mortality in mild, moderate and severe events was 3.8%, 6.9% and 13.9%, respectively. Most clinical parameters indicated a significantly worse condition in patients classified in the severe group, compared to those in mild or moderate groups.
Conclusion: Most of the events, traditionally all classified as severe because of the hospitalization, were classified as moderate, while almost 15% were mild. The results of this study provide insight in the heterogeneity of hospitalized ECOPD and show that the newly proposed Rome criteria can differentiate between events with different short-term mortality rates.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is the most prevalent chronic respiratory disease worldwide and is associated with significant health and economic burden. Despite available treatments, COPD cannot be cured, and it is one of the major leading causes of death across the globe [1]. A significant proportion of patients with COPD suffers from exacerbations (ECOPD), which are traditionally defined as an acute worsening of respiratory symptoms resulting in additional therapy [2]. ECOPD contribute to lung function deterioration [3], poor health status [4, 5], deconditioning [6] and premature mortality [7]. The vast majority of ECOPD is treated in outpatient setting, but hospitalization may be warranted in severe events [8] and these are associated with even worse outcomes [7]. According to the traditional severity classification for ECOPD, mild events are those treated with short acting bronchodilators (SABDs); moderate events require antibiotics, systemic corticosteroids or both; and severe events are those requiring admission to an emergency room or hospitalization [2]. Thus, severity of ECOPD is usually graded *post hoc*, based on what medications were used to control symptoms and in what setting [2]. As management of ECOPD may differ according to local protocols and financing of care, and availability and access to healthcare, clinical heterogeneity within each of the three severity ECOPD classes is anticipated. For example, the absence of family caregivers or severe anxiety associated with increased dyspnea, may contribute to an indication for hospitalization and therefore the classification of the ECOPD as severe, irrespective of objective measures of respiratory status. Next to this, different hospitals, physicians, and patients may have different individual preferences or habits that influence treatment decisions, especially across the globe and cultures.

Recently, a new severity classification of ECOPD was proposed by a group of international COPD experts [9]. In this new classification, named the Rome proposal, six objectively measured variables are used to mark the event severity: dyspnea (assessed by visual analog scale [10] [on a scale of 0–10] ≥5), oxygen saturation (Sa_{O2}), respiratory rate, heart rate, serum C-reactive protein (CRP) and, in selected cases, arterial blood gases. Based on these variables, ECOPD are subsequently classified as mild (low dyspnea, low breathing rate, low heart rate, normal oxygen saturation, low CRP), moderate (3 of the following: high dyspnea, high respiratory rate, high heart rate, low oxygen saturation, high CRP) or severe (hypercapnia and acidosis) (Table S1) [9].

The distribution of a real-world population of patients with ECOPD according to the traditional classification across the newly proposed severity classification is currently unknown. Resulting from the lack of objective criteria in the traditional classification, we assume that a significant proportion of hospitalized patients will have a mild or moderate event according to the Rome classification. Moreover, in-hospital, 30- and 90-days mortality of patients stratified according to the Rome severity

classification are unknown. This may have important implications for the clinical implementation of this new classification, for the perception of these events by patients and healthcare workers, for the impact on health care costs and for the interpretation of clinical COPD studies using severe ECOPD as an outcome. The aim of this study is therefore to apply the Rome severity classification to a real-world population of patients with hospitalized ECOPD according to the traditional classification and subsequently, compare the clinical implementation of the two classifications.

Methods

The present study concerns a *post hoc* analysis on a previously published study in which data of a real-world cohort of COPD patients hospitalized with a severe ECOPD, was used to develop a risk stratification tool for severe ECOPD [11]. In the current study, the Rome severity classification was applied to this cohort, which consisted of 364 patients admitted to the Department of Respiratory Medicine of Maastricht University Medical Center (MUMC), the Netherlands, between 1 June 2011 and 31 December 2014. Demographics, vital and physical signs, laboratory results, arterial blood gases and phenotypic disease characteristics were available for all patients. Moreover, in-hospital and 30- and 90-days all-cause mortality were recorded. Patient identification as well as in- and exclusion criteria were previously described [11]. Because of the use of de-identified clinical data ethical approval was not necessary according to the local ethical committee (METC 13-4-041).

Study design

First, the Rome criteria were applied to the cohort. Since severe dyspnea (VAS ≥5) is the most common symptom in patients hospitalized for ECOPD [12, 13], generally considered the most relevant symptom for most ECOPD [9] and no visual analog scale (VAS) was available to quantify dyspnea in this cohort, a positive score of this item of the severity classification was assumed in all patients. Moreover, differences in in-hospital, 30- and 90-days mortality were compared between mild, moderate and severe ECOPD according to the new classification. Thereafter, the different severity classes were compared regarding general disease characteristics and clinical parameters.

Statistical analysis

Statistical analysis was performed with IBM SPSS version 28.0 software for Windows (IBM Corporation, Armonk, NY, USA). First descriptive analysis was performed. Thereafter a frequency distribution was generated through applying the Rome severity classification to this COPD cohort. Moreover, data was stratified by the different severity classes and compared regarding general disease characteristics and clinical parameters. Variables were subjected to the Shapiro-Wilk normality test. For normally distributed variables, one-way ANOVA followed by Tukey's test was

performed to indicate differences between severity classes. For non-parametric data, Kruskal-Wallis followed by Dunn's with a Bonferroni correction for multiple comparison was applied. Categorical variables were compared by Pearson's chi-square test or the Fisher's exact test, as appropriate, followed by Bonferroni adjustment. P-values of <0.05 were considered to indicate statistical significance.

Results

Characteristics of hospitalized ECOPD cohort

As presented in table 1, the study population consisted of an almost even distribution of elderly male and female patients. A substantial proportion was current smoker. The majority of patients had severe airflow limitation. More than half of the population needed support and extra care with daily living, while most lived in their own home. Moreover, more than 50% of patients were previously admitted to the hospital with an ECOPD, whereas almost one in four had a previous admission for an ECOPD in the last two years.

Table 1 Demographics and clinical characteristics of 364 patients admitted to the hospital with an ECOPD prior to admission

Characteristics	n (%)
Age (years)	70.5 ± 10.2
Age ≥ 80 (years)	79 (21.7)
Gender, male	169 (46.4)
Current smoker	132 (37.0)
Gold-stage	
1. $FEV_1 \geq 80\%$	10 (2.7)
2. $50\% \leq FEV_1 < 80\%$	119 (32.7)
3. $30\% \leq FEV_1 < 50\%$	170 (46.7)
4. $FEV_1 < 30\%$	65 (17.9)
Comorbidities	
Charlson's index	2.22 ± 1.44
Supported living and extra care	185 (53.0)
Cohabiting	196 (59.0)
Residence status	
Own home	292 (83.2)
Retirement home	47 (13.4)
Other	12 (3.4)
Previous admission ever	204 (56.0)
Admission last 2 years	
- 0	203 (55.8)
- 1	89 (24.4)
- 2	35 (9.6)
- ≥3	37 (10.2)

Data reported as n (%) or mean with standard deviation depicted after ±. Abbreviation: FEV_1: forced expiratory volume in one second.

Application of Rome severity classification to patient cohort hospitalized with ECOPD

The traditional severity classification categorizes the severity of ECOPD of all 364 patients as severe, as they all have been hospitalized due to the event. In contrast, when implementing the criteria of the Rome proposal, 52 (14.3%) patients had a mild ECOPD, 204 (56.0%) patients a moderate and 108 (29.7%) patients a severe ECOPD (table 2). In addition, out of 31 patients who died in-hospital 14 (3.8%) patients had a moderate ECOPD, while 15 (4.1%) patients were classified as severe. Thus, in-hospital mortality in mild, moderate and severe events was 3.8%, 6.9% and 13.9%, respectively. The proportion of patients that died at days 30 and 90 was highest in the group of severe ECOPD, but nonetheless deaths were also observed in the mild and moderate events (30 days: mild 7.7%, moderate 7.4%, severe 17.6%; 90 days: mild 7.7%, moderate 13.7%, severe 25.0%). Almost half of the population lived on their own and especially patients in the severe group (60.5%) received extra care.

Table 2 Stratification of Rome severity classification across hospitalized COPD cohort with ECOPD

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

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

Rome proposal criteria and clinical characteristics stratified by ECOPD severity

The results for the individual items of the newly proposed Rome criteria for the three different severity classes are shown in table 3. As mentioned in the methods, it was assumed that all hospitalized patients suffered from severe dyspnea. Except for serum CRP, mean values of all parameters indicated a significantly worse condition in patients classified in the severe group, compared to those in mild or moderate groups. According to the Rome proposal, acidosis and hypercapnia are the two criteria to indicate a severe ECOPD. Our analysis shows that both were statistically different from mild and moderate events ($p<0.001$). Mean HR, RR, CRP and SaO_2 levels for mild events were significantly different from those of moderate and severe (table S2). Except for $PaCO_2$ and pH, the mean value of the other variables did not differentiate between moderate and severe ECOPD.

Table 3 Criteria for determining ECOPD severity according to Rome proposal.

Criteria (n)	**Mild**	**Moderate**	**Severe**	**P value†**
Dyspnoea* (52/204/108)	52 (100.0)	204 (100.0)	108 (100.0)	
HR, bpm	84.3 ± 16.2	101.3 ± 18.0	106.9 ± 24.2	<0.001
HR ≥ 95 (51/200/106)	6 (11.8)	133 (66.5)	74 (69.8)	
RR, breaths/min	19.0 ± 4.3	24.9 ± 5.2	26.9 ± 7.0	<0.001
RR ≥ 24 (14/99/60)	2 (14.3)	69 (69.7)	42 (70.0)	
Resting SaO_2%	89.2 ± 6.7	86.8 ± 6.0	83.2 ± 11.1	<0.001
SaO_2 < 92% (48/203/106)	21 (43.8)	163 (80.3)	86 (81.1)	
CRP levels, mg/L	20.0 ± 33.4	81.3 ± 86.6	75.7 ± 98.0	<0.001
CRP ≥ 10 (51/203/107)	17 (33.3)	178 (87.7)	79 (73.8)	
ABG PaO_2, mmHg	66.8 ± 25.9	57.0 ± 12.6	66.3 ± 35.0	0.022
PaO_2 ≤ 60 (48/203/107)	18 (37.5)	136 (67.0)	57 (53.3)	
ABG $PaCO_2$, mmHg	45.4 ± 9.7	45.0 ± 12.4	69.5 ± 18.2	<0.001
$PaCO_2$ > 45 (51/203/108)	22 (43.1)	82 (40.4)	102 (94.4)	
pH	7.42 ± 0.04	7.42 ± 0.04	7.26 ± 0.07	<0.001
pH < 7.35 (51/203/108)	-	-	108 (100.0)	
Nr. of positive criteria	1.88 ± 0.32	3.66 ± 0.68	3.60 ± 0.98	

Data presented as n (%) and mean with standard deviation depicted after ±.
*Dyspnoea score was missing in database; a positive score of this item was assumed in all patients.
ABG, arterial blood gas; bpm, beats per minute; CRP, C-reactive protein; HR, heart rate; RR, respiratory rate; SaO_2, oxygen saturation measured in arterial blood gas;
†, Kruskal-Wallis

Table 4 shows demographics, lung function, comorbidities and other clinical and laboratory parameters for patients stratified according to the Rome classification. Age, gender distribution, BMI and smoking status were comparable between groups. More than 50 percent of patients in the three severity categories were previously admitted to the hospital during their lifetime, of which patients with a mild ECOPD had the highest comorbid index. Results from spirometry, body box and diffusion measurements differed between groups; especially, results from FEV_1 and FEV_1 pred% for the severe group were significantly lower compared to mild and moderate ECOPD (table S3). Additionally, it was apparent that a significantly higher proportion of patients with a severe ECOPD was in the need of extra oxygen while being hospitalized. Lastly, radiologic abnormalities were more frequently observed in patients classified as severe (table S3).

Table 4 Clinical parameters stratified by Rome severity classification

Characteristics (n)	**Mild**	**Moderate**	**Severe**	**P value**[†]
Age	72.8 ± 10.0	70.2 ± 10.3	70.1 ± 10.0	0.221[°]
Gender, male (52/204/108)	27 (51.9)	90 (44.1)	52 (48.1)	0.549
BMI, kg/m2	24.4 ± 5.2	25.2 ± 6.2	24.8 ± 7.2	0.608
Smoking status				
current smoker (51/202/104)	21 (41.2)	69 (34.2)	42 (40.4)	0.451
Gold-stage (52/204/108)				
1. $FEV_1 \geq 80\%$	3 (5.8)	7 (3.4)	-	0.056*
2. $50\% \leq FEV_1 < 80\%$	21 (40.4)	70 (34.4)	28 (25.9)	
3. $30\% \leq FEV_1 < 50\%$	20 (38.5)	95 (46.6)	55 (50.9)	
4. $FEV_1 < 30\%$	8 (15.4)	32 (15.7)	25 (23.1)	
Lung function				
FEV_1 litres	1.2 ± 0.5	1.1 ± 0.5	0.9 ± 0.3	0.004
FEV_1 pred%	50.4 ± 19.7	46.4 ± 17.2	40.5 ± 12.9	0.004
FEV_1 / FVC	45.3 ± 12.8	41.9 ± 12.0	39.1 ± 10.5	0.013
Diffusion				
DLCO/SB pred%	47.7 ± 19.1	49.4 ± 18.3	40.8 ± 15.1	0.009
Previous admission				
Admission ever (52/204/108)	26 (50.0)	118 (57.8)	60 (55.6)	0.592
Admission last 2 years				
An admission (52/204/108)				0.354
0	31 (59.6)	107 (52.5)	65 (60.2)	0.342
1	8 (15.4)	61 (29.9)	20 (18.5)	
2	5 (9.6)	20 (9.8)	10 (9.3)	
≥ 3	8 (15.4)	16 (7.8)	13 (12.0)	
Comorbidities				
Charlson's index	2.65 ± 1.6	2.08 ± 1.3	2.28 ± 1.5	0.035
CCI category				
CCI 1-2 points (52/204/108)	30 (57.7)	143 (70.1)	72 (66.7)	0.231
CCI ≥ 3 points (52/204/108)	22 (42.3)	61 (29.9)	36 (33.3)	
Vital signs				
Temperature, C	36.9 ± 0.7	37.5 ± 0.9	37.0 ± 1.1	<0.001
Systolic BP, mmHg	140.8 ± 26.5	137.9 ± 25.0	145.6 ± 28.3	0.070
Diastolic BP, mmHg	77.2 ± 17.0	75.1 ± 15.7	79.8 ± 16.7	0.106
Extra FiO_2 (46/177/91)	16 (34.8)	68 (38.4)	58 (63.7)	<0.001
Physical examination				
Confused (2/15/10)	1 (50.0)	3 (20.0)	4 (40.0)	0.338*
Use of accessory muscles (3/15/16)	1 (33.3)	14 (93.3)	15 (93.8)	0.031*
Elevated CVP (20/62/37)	2 (10.0)	7 (11.3)	11 (29.7)	0.050*
Peripheral oedema (42/180/85)	12 (28.6)	47 (26.1)	29 (34.1)	0.404
Wheezing (50/202/108)	36 (72.0)	120 (59.4)	56 (51.9)	0.056
Crackles (50/202/108)	13 (26.0)	63 (31.2)	39 (36.1)	0.421
Blood eosinophils, %	1.3 ± 2.1	0.7 ± 1.6	1.4 ± 2.4	0.107
Troponin >14 ng/L (52/204/108)	7 (13.5)	48 (23.5)	34 (31.5)	0.041
NT-proBNP pmol/L	323.7 ± 582.6	405.9 ± 621.4	518.7 ± 678.1	0.057
NT-proBNP ≥ 500 pmol/L	2 (11.8)	13 (17.8)	16 (32.7)	0.105*

(17/73/49)				
Chest X-ray				
Consolidation (51/204/108)	5 (9.8)	69 (33.8)	33 (30.6)	0.003
Signs of congestion (51/204/108)	3 (5.9)	23 (11.3)	26 (24.1)	0.002
ECG				
Atrial fibrillation (47/183/99)	6 (12.8)	20 (10.9)	17 (17.2)	0.332
Signs of ischaemia (47/183/99)	2 (4.3)	10 (5.5)	10 (10.1)	0.272*

Data presented as n (%) or mean with standard deviation depicted after ±.
BMI, body mass index; BP, blood pressure; CCI, Charlson's comorbidity index; CVP, central venous pressure; DLCO/SB, single-breath diffusing capacity of the lung for carbon monoxide; ECG, electrocardiogram; FEV_1, forced expiratory volume in 1s; FEV_1/VC, ratio FEV_1/VC; FiO_2, fraction of inspired oxygen; NT-proBNP, brain natriuremic peptide; pred%, percentage of predicted value; RV/TLC, ratio residual volume and total lung capacity; SpO_2, oxygen saturation measured by pulse oximetry.
† Kruskal-Wallis unless otherwise stated
° One-way ANOVA
* Fisher's exact test

Discussion

This study showed that only a minority of patients hospitalized with ECOPD fulfilled the newly proposed Rome criteria for a severe event. Most of the events, traditionally all classified as severe because of the hospitalization, were classified as moderate, while almost 15% were mild. In-hospital and post-discharge mortality were highest in patients with severe ECOPD, although >10% of patients with mild to moderate ECOPD died within 90 days after hospitalization. Patients with severe ECOPD had more severe underlying COPD and received more extra care. The latter indicates a higher burden of disease prior to the ECOPD. Those with mild ECOPD were slightly older and had more comorbidities. It can be speculated that these factors contributed to the indication for hospitalisation in these milder ECOPD. The results of this study provide insight in the heterogeneity of hospitalized ECOPD and show that the newly proposed Rome criteria can differentiate between events with different short-term mortality rates.

It is well-acknowledged that the traditional severity classification of ECOPD results in substantial variability in clinical characteristics of patients with hospitalized events. This hinders the interpretation of interventional studies which use hospitalizations as an outcome and the efforts to study the pathophysiology and predictors of ECOPD within the hospital setting. The Rome classification resulted from a Delphi process during which a group of international COPD experts selected six measured variables as markers of event severity, based on thorough literature review and discussion. The implementation of objective, easy and ready to measure variables in this proposed classification may contribute to a better delineation of clinically different ECOPD. Also, this may aid in differentiating ECOPD from other conditions with similar symptoms. Indeed, differences in

comorbidities and radiologic abnormalities between severity classes were observed in the current study. Moreover, implementation of these criteria may facilitate clinical decision making if it can be demonstrated that objectively-identified mild and/or moderate events are associated with better outcomes than severe ECOPD. Ultimately, these criteria could be used as a basic set for reimbursement of costs related to hospitalizations.

As expected, heart rate and respiratory rate were significantly elevated in patients with a moderate and severe ECOPD compared to patients with a mild event, since the Rome classification is largely based on differences in these parameters. Several studies showed that both an elevated heart [14-16] and respiratory rate [17-19] were predictive variables for the severity of an ECOPD. Jensen et al. showed that an increase in resting heart rate is associated with severity of COPD and correspondingly mortality risk [20]. These two variables are easily and non-invasively measured, and of great value grading the respiratory status and with that, ECOPD severity [15, 21-23]. Serum CRP values were highest during moderate events, with 87.7 percent of patients having a CRP above 10 mg/L. Although measuring CRP levels as a marker of airway inflammation may lack specificity, it is widely recognized as an useful and sensitive marker of infections and ECOPD [24]. The current analysis suggests that a cut-off value of 10 mg/L lacks sensitivity to distinguish between moderate and severe events. Also, clinical parameters were largely comparable between events characterized as moderate or severe. This suggests that the Rome classification mainly enables differentiation between mild and more severe ECOPD. Furthermore, this study showed that patients with a severe ECOPD demonstrated lower SaO_2 levels, 81.1% of patients had a SaO_2 <92%. This corresponds to other studies which showed that a reduction in oxygen saturation was associated with ECOPD risk [14-16]. It should be noted that the extent of change is important for early ECOPD detection. The Rome proposal uses a change of 3% to distinguish mild versus moderate events. More studies are needed to pinpoint the correct change in SaO_2 to assess ECOPD risk. Additionally, ABG showed hypercapnia in 94.4% of patients and acidosis in all patients during a severe episode. These are mostly serious complications observed in patients in the advanced phase of COPD [25], the lower the pH the higher the mortality risk [26-28]. While measuring ABG is more reliable than pulse oximetry, it is less practical and not widely available in all clinical settings.

As for the clinical parameters it was apparent that general characteristics such as age, gender, smoking status and BMI did not significantly differ in our analysis between the different severities. Identifying the GOLD stage of patients mostly offers clinicians valuable information to implement appropriate treatment. Results from routine lung function tests were significantly different between the three ECOPD severities. Nonetheless, a great number of patients are not able to complete pulmonary function testing because of their poor health conditions [29]. Next to this,

several biomarkers such as blood eosinophilia, troponin and NT-proBNP levels were elevated for patients having a severe event. Eosinophil levels have until now not been used to determine ECOPD severity but can give an indication whether systemic corticoids should be given to treat a patient [30]. Troponin and NT-proBNP are mainly associated with heart failure which can be a confounding comorbidity or may coexists with an ECOPD [9, 31]. Another inflammatory mediator that is associated with ECOPD are neutrophils, as ECOPD are an acute burst of local or systemic inflammatory mediators [29]. These cells are the most abundant inflammatory cells found in blood and sputum. Numbers increase while having an ECOPD and could therefore be a valuable parameter to indicate severity [32, 33].

Our analysis shows that significantly more patients with a severe ECOPD received extra oxygen while being hospitalized compared to patients with a mild or moderate event. This can be a valuable additional marker to mark event severity. In a larger number of cases, chest X-ray showed signs of congestion and consolidation in the moderate and severe group. This suggests that other clinical conditions including heart failure and pneumonia, complicate the ECOPD and contribute to event severity. While it could be argued that these patients did not have a strict diagnosis of ECOPD, these results reflect the real-life clinical setting of the studied cohort. As such, it may be considered to add the presence of other acute conditions to a severity classification for ECOPD. The current study also suggests that it is important to perform additional clinical evaluations, imaging and biomarker measurements to diagnose other conditions [34, 35].

This study has several limitations that need to be addressed. First, data from this clinical COPD cohort were obtained from a single centre in the Netherlands, meaning that the results are likely different for other COPD populations, hospitals or healthcare settings/systems with different disease severity and protocols for hospitalization and management of ECOPD. Also, the cohort only included hospitalized patients, so the potential contribution of the Rome criteria in clinical decision-making regarding hospitalization or not at the emergency room remains unknown. The assumption of VAS ≥5 resulted in a minimum of 1 positive criterium in all patients and a shift towards more moderate events. Several other studies in patients hospitalized for ECOPD indicated that severe dyspnea is indeed the most important symptom in this setting [12, 13], supporting the assumption of the current study. Also, this assumption did not affect the proportion of patients with severe ECOPD as VAS is no criterium for that. Since the change of 3% in resting SaO_2 for mild versus moderate events and the time frame for development of symptoms (within 14 days according to the Rome definition experts[9]) were not determined and therefore not included in our analyses. Lastly, this study is partly focused on the relationship between ECOPD severity and 30- and 90-days in-hospital

mortality. Data on mortality for a longer time period was not available for this study. Hospital readmission is also an important outcome parameter that can influence ECOPD severity, and subsequently, mortality. Data for this was not available but should be taken into account in future studies.

The traditional severity classification has several shortcomings that may negatively affect clinical and healthcare decisions. The current Rome criteria are all readily measurable and provide objective measurements of symptoms, signs, biomarkers and physiological variables. However, according to data from the BACE (Azithromycin for Acute Exacerbations Requiring Hospitalization) study [36], 3 moderate criteria were met by 70% of hospitalized patients due to an ECOPD, 4 moderate criteria by 36.4% and 5 criteria by 6.9%. Only 8.3% of patients met the criteria belonging to a severe event. In the current analysis, most ECOPD were classified as moderate and almost 30% as severe. Ramakrishnan et al. stressed that the different endotypes of ECOPD severity cannot be assessed by solely focusing on inflammatory and pathophysiological parameters [37]. Interestingly, the current results showed that a remarkably high percentage (>10%) of patients with a mild to moderate event died within 30 or 90 days after hospitalization. This raises questions whether an ECOPD can be interpreted as either mild or moderate, instead of severe. Nevertheless, it is known that the main causes of death in mild and moderate COPD are mostly lung cancer or cardiovascular diseases [38]. From our analysis, patients with a mild ECOPD showed the highest comorbid index, which could indicate that they have been hospitalized because of their comorbidity rather than the severity of their acute respiratory event. Therefore, it can be debated whether merely the Rome criteria can be used as an indicator for hospitalization of ECOPD. In more severe COPD, respiratory failure is the primary cause [38]. Next to comorbidities and acute respiratory failure, the GOLD 2023 strategy document states that other potential indications for hospitalization could be the onset of new physical signs such as cyanosis and peripheral oedema, failure of an AECOPD to respond to initial medical management and insufficient home support [2]. These are currently not considered in the Rome classification.

Until now, there exists no universal marker to specify an ECOPD, and with that ECOPD cause. Clinical parameters such as GOLD stage, eosinophil or neutrophil levels and receiving extra oxygen could be integrated as additional criteria to assess ECOPD occurrence and severity. It is important to consider COPD as a multicomponent disease and take all-cause mortality as one of the major endpoints in order to apply appropriate therapy. The Rome proposal criteria are the first step to differentiate between clinically different ECOPD, which may in turn be of value in differentiating ECOPD from other conditions with similar symptoms. Next to this, the traditional grading of ECOPD severity is merely based on medication use and hospitalizations and thus required refinement. The

implementation of objective variables in the newly proposed severity classification will better inform clinical and healthcare decisions as well as the interpretation of results in research. Although the Rome proposal may still need refinement in selection of variables and corresponding thresholds, this study provided important initial insights in the distinctive and predictive value of the proposed classification and is an important step towards a change of the traditional ECOPD severity classification.

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Supplements

Table S1. Rome proposal criteria for classifying the severity of ECOPD

Severity	Criteria for assessing ECOPD severity
Mild	• Dyspnea VAS <5 • RR <24 breaths/min • HR <95 bmp • Resting SaO_2 ≥ 92%* and change ≤3% • CRP <10 mg/L
Moderate (at least three out of five)†	• Dyspnea VAS ≥5 • RR ≥24 breaths/min • HR ≥95 bpm • Resting SaO_2 <92%* and/or change >3% • CRP ≥10 mg/L
Severe	• ABG demonstrate hypercapnia and acidosis ($PaCO_2$ >45 mmHg and pH <7.35)

* : Patient breathing ambient air or the usual oxygen prescription.

† : In addition, if obtained, ABG may show hypoxemia (PaO_2 ≤60 mmHg), hypercapnia ($PaCO_2$ >45 mmHg) or both, but no acidosis (pH >7.35)

ECOPD= exacerbation of chronic obstructive pulmonary disease; VAS= visual analog scale; RR= respiratory rate; HR= heart rate; CRP= C-reactive protein; ABG=arterial blood gases

Table S2. Between-group differences of Rome proposal criteria within ECOPD severity classes

Group comparisons	**Mild-Moderate**[±]	**Mild-Severe**[±]	**Moderate-Severe**[±]	**P value**[†]
HR, bpm	<0.001	<0.001	0.190	<0.001
RR, breaths/min	0.001	<0.001	0.292	<0.001
Resting SaO_2%	0.010	<0.001	0.063	<0.001
CRP levels, mg/L	<0.001	<0.001	0.131	<0.001
ABG PaO_2, mmHg	0.017	0.161	1.000	0.022
ABG $PaCO_2$, mmHg	1.000	<0.001	<0.001	<0.001
pH	1.000	<0.001	<0.001	<0.001

ABG, arterial blood gas; bpm, beats per minute; CRP, C-reactive protein; HR, heart rate; RR, respiratory rate; SaO_2, oxygen saturation measured in arterial blood gas;

† Kruskal-Wallis

± Dunn's Bonferroni

Table S3. Between-group differences of clinical parameters

Characteristics (n)	**Mild/Moderate±**	**Mild/Severe±**	**Moderate/Severe±**	**P value†**
Lung function				
FEV_1 litres	0.944	0.011	0.015	0.004
FEV_1 pred%	0.623	0.007	0.023	0.004
FEV_1 / FVC	0.350	0.014	0.143	0.013
Body box				
RV/TLC pred%	0.131	0.003	0.122	0.004
Diffusion				
DLCO/SB pred%	1.000	0.376	0.007	0.009
Comorbidities				
Charlson's index	0.029	0.238	1.000	0.035
Vital signs				
Temperature, C	<0.001	0.648	0.003	<0.001
Extra FiO_2 (46/177/91)	1.000	0.004	<0.001	<0.001
Physical examination				
Use of accessory muscles (3/15/16)	0.056	0.051	1.000	0.031*
Elevated CVP (20/62/37)	1.000	0.111	0.031	0.040*
Troponin >14 ng/L (52/204/108)	0.133	0.043	0.139	0.041°
Chest X-ray				
Consolidation (51/204/108)	0.002	0.013	0.613	0.003°
Signs of congestion (51/204/108)	0.312	0.017	0.009	0.002°

Data represent the p-values for between-group differences. Three groups were compared with each other: mild/moderate, mild/severe and moderate/severe. BMI, body mass index; BP, blood pressure; CCI, Charlson's comorbidity index; CVP, central venous pressure; DLCO/SB, single-breath diffusing capacity of the lung for carbon monoxide; ECG, electrocardiogram; FEV_1, forced expiratory volume in 1s; FEV_1/VC, ratio FEV_1/VC; FiO_2, fraction of inspired oxygen; NT-proBNP, brain natriuremic peptide; pred%, percentage of predicted value; RV/TLC, ratio residual volume and total lung capacity; SpO_2, oxygen saturation measured by pulse oximetry.

† Kruskal-Wallis, unless otherwise stated

± Dunn's Bonferroni, unless otherwise stated

° Chi-square

* Fisher's exact test

Bonferroni-adjusted p-values 0.05/3=0.017