

# Applying the Rome Proposal on Exacerbations of Chronic Obstructive Pulmonary Disease: Does Comorbid Chronic Heart Failure Matter?

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**Background:** Chronic heart failure (CHF) is a common comorbidity among patients with chronic obstructive pulmonary disease (COPD). Both exacerbations of COPD (ECOPDs) and exacerbations of CHF (ECHFs) display worsening of breathlessness at rest (BaR) and breathlessness at physical activity (BaPA). Comorbid CHF may have an impact on the vital signs assessed, when the Rome proposal (adopted by GOLD 2023) is applied on ECOPDs. Thus, the aim of the present study was to investigate the impact of comorbid CHF on ECOPDs severity, particularly focusing on the influence of comorbid CHF on BaR and BaPA.

**Methods:** We analysed data on COPD symptoms collected from the telehealth study The eHealth Diary. Patients with COPD (n = 43) and patients with CHF (n = 41) were asked to daily monitor BaR and BaPA, employing a digital pen and scales for BaR and BaPA (from 0 to 10). Twenty-eight patients of the COPD patients presented with comorbid CHF. Totally, 125 exacerbations were analysed.

**Results:** Exacerbations in the group with COPD patients and comorbid CHF were compared to the group with COPD patients without comorbid CHF and the group with CHF patients. Compared with GOLD 2022, the GOLD 2023 (the Rome proposal) significantly downgraded the ECOPD severity. Comorbid CHF did not interfere significantly on the observed difference. Comorbid CHF did not worsen BaR scores, assessed at inclusion and at the symptom peak of the exacerbations.

**Conclusion:** In the present study, we find no evidence that comorbid CHF would interfere significantly with the parameters included in the Rome proposal (GOLD 2023). We conclude that the Rome proposal can be safely applied even on COPD patients with very advanced comorbid CHF.

**Keywords:** chronic heart failure, telemonitoring, telemedicine, COPD symptoms

## Introduction

Most patients with more advanced chronic obstructive pulmonary disease (COPD) present with breathlessness as a typical symptom.<sup>1</sup> Breathlessness, either displayed at rest (BaR) or at physical activity (BaPA), is a consequence of chronic airflow limitation (CAL) and hyperinflation,<sup>2</sup> the latter being a result of alveolar wall destruction and development of emphysema.<sup>3</sup> CAL, on the other hand, is due to an airway inflammation, which is usually dominated by neutrophils,<sup>4</sup> and a sub-epithelial fibrosis, which is driven by epithelial–mesenchymal transition.<sup>5</sup> Metabolic disturbances of cells' handling of iron, relevant for the resistance against oxidative damage,<sup>6,7</sup> and muscle tissue bioenergetics, important for normal muscle function, are some mechanisms implicated in COPD pathogenesis.<sup>8</sup>

Possibly, due to a progression from a local airway inflammation to a systemic one, COPD may involve muscle cells in skeletal muscles, causing myosteatosis, which in turn trigger BaPA by a reduced physical performance.<sup>8,9</sup> In addition to common risk factors, such as smoking and advanced age, a low-grade systemic inflammation is thought to be involved in the pathogenesis of chronic heart failure (CHF).<sup>10</sup> CHF is a common comorbidity among patients with COPD with an estimated prevalence of 5–41%.<sup>11,12</sup> Both COPD and CHF lead to a varying degree of BaR and BaPA in affected

individuals. As exacerbations can occur in both COPD and CHF, it can be challenging to differentiate between exacerbations of COPD (ECOPD) and exacerbations of CHF (ECHF). This is especially true when the onset of deterioration is represented by breathlessness only.<sup>13</sup>

An ECOPD is defined as an event characterized by breathlessness and/or cough and sputum that worsen over  $\leq 14$  days.<sup>14</sup> ECOPDs are often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insults to the lungs.<sup>14</sup> The severity of an ECOPD is determined in the GOLD 2023 guidelines and dictated by the Rome Proposal.<sup>14,15</sup> The latter grades BaR on a scale from 0 to 10. The updated definition aims to overcome the limitations of the previous definition, that is GOLD 2022, which defines ECOPD severity by the medical actions needed to take.<sup>15</sup> Thus, the Rome proposal has the potential to improve clinical care and research.<sup>15</sup> However, it needs to be urgently validated by clinical studies.<sup>16</sup>

In the present study, the aim was to investigate the influence of comorbid CHF on ECOPD severity when assessed by the GOLD 2023, according to the Rome proposal, and by the GOLD 2022. Moreover, we tested whether comorbid CHF had a significant impact on how study patients with COPD would score BaR and BaPA at study inclusion and during ECOPDs.

## Materials and Methods

### Study Subjects and Study Procedures

The eHealth Diary, which is a longitudinal telemonitoring study conducted in Östergötland, Sweden between 2013 and 2017, provided the data analysed in the present study.<sup>17–21</sup> In that previous study patients with COPD and CHF, who were frequently hospitalised due to ECOPDs or ECHFs, were included. The eHealth Diary study utilised the Health Diary telemonitoring system, which relied on digital pen technology for patient reporting on daily health status to a specialised hospital-based home care (HBHC) unit. COPD participants were asked to record their COPD symptoms every day on a scale from 0 to 10. CHF patients used the same scale for monitoring BaR and BaPA daily, but they were also asked to record their weight daily.

The HBHC unit was responsible for providing healthcare during the study period. The diagnosis of the ECOPDs and the ECHFs was based on the symptom registrations from the study participants, together with an assessment by the experienced physicians at HBHC. When the HBHC staff detected a deterioration in symptoms, they visited the patients at their homes, and, if the physician diagnosed an ECOPD or an ECHF, treatment was then started with antibiotics and/or steroids or diuretics. In the present study, data from patients with at least one symptom registration was included in the analysis ( $n = 84$ ). Included patients were divided in two groups: those with COPD ( $n = 43$ ) and those with CHF ( $n = 41$ ). The group with COPD patients, was subdivided in two groups, those without comorbid CHF ( $n = 15$ ) and those with comorbid CHF ( $n = 28$ ). Among COPD patients with comorbid CHF, COPD was the dominating disease and was the main cause behind previous hospitalisations.

### Assessments at Inclusion and During Exacerbations

At inclusion, all patients had age, gender and smoking habits recorded. Body-mass-index (BMI) (weight in kg divided by the height in  $m^2$ ) was calculated.<sup>22</sup> Comorbidities were graded, using the Charlson Comorbidity Index' (CCI).<sup>23</sup> Blood oxygen saturation (SAT) was also measured.

At inclusion, patients with COPD had the severity of airway obstruction measured with dynamic spirometry after bronchodilatation. Thus, forced expiratory volume in 1 second ( $FEV_1$ ) and forced vital capacity (FVC) and the ratio of these volumes were analysed using Hedenström as a reference.<sup>24,25</sup> CAL was defined as  $FEV_1/FVC < 70\%$  after bronchodilatation and airway obstruction was graded according to GOLD 2023;<sup>14</sup> thus,  $FEV_1\%$  predicted 80–100% was stage 1, 50–79% was stage 2, 30–49% was stage 3, and 0–29% was stage 4. Patients were also classified according to GOLD 2023<sup>14</sup> as A, B and E, depending on symptom burden and frequency of ECOPDs. During ECOPDs ( $n = 107$ ) we assessed BaR, BaPA, respiratory rate (RR), heart rate (HR), SAT, CRP, and arterial blood gases (ABG), the latter at rest on air breathing or ongoing oxygen supplementation. The therapy started to treat the ECOPD was documented. The Rome proposal states that the BaR values should range from 0 to 3 when the COPD patient is in a stable phase.<sup>15</sup>

At inclusion, CHF patients had the severity of HF graded according to the New York Heart Association (NYHA) classification and by a previous assessment of the left ventricular ejection fraction (LVEF), employing echocardiography. CHF was defined according to the latest European Society of Cardiology (ESC) guidelines.<sup>26</sup> CHF with reduced ejection fraction (HFrEF), with mid-range ejection fraction (HFmrEF) and with preserved ejection fraction (HFpEF) displayed LVEF <40%, 40–49% and ≥50%, respectively. Additional criteria for the latter were dyspnoea, serum NT-proBNP >125 pg/mL, and structural heart disease, such as left ventricular hypertrophy and/or left atrial enlargement, and/or diastolic dysfunction. During ECHFs (n = 18 in the CHF-group), BaR, BaPA and SAT deteriorated, while HR and body weight were increased. The therapy started to treat the ECHF was documented.

## COPD Exacerbation Severity According to GOLD 2022 and 2023

The severity of all ECOPDs was determined according to the criteria of GOLD 2022, which defines the severity by the medical action needed. Thus, a mild ECOPD requires increased inhalation therapy only, a moderate ECOPD demands additional therapy with antibiotics and/or steroids, while a severe ECOPD leads to surveillance and treatment at the emergency room and/or hospitalisation. When hospitalisation is needed, this is often because of a demand of oxygen supplementation or assisted ventilation or both.

The severity of all ECOPDs was also determined by the definitions provided by GOLD 2023 and dictated by the Rome proposal.<sup>15</sup> In GOLD 2023, ECOPD severity is determined by various parameters, including BaR, RR, HR, SAT, CRP, and ABG. Mild exacerbations are defined as having BaR <5, RR <24 breaths/min, HR <95 bpm, resting SAT ≥92% breathing ambient air (or patient's usual oxygen prescription) and change ≤3% (when known), CRP <10mg/L (if obtained). Moderate exacerbations are defined by at least three out of five parameters, including BaR ≥5, RR ≥24 breaths/min, HR ≥95 bpm, resting SAT <92% breathing ambient air (or patient's usual oxygen prescription), and/or change >3% (when known), CRP ≥10mg/L. Additionally, ABG may show hypoxemia (PaO<sub>2</sub> ≤8 kPa) and/or hypercapnia (PaCO<sub>2</sub> >6 kPa) but no acidosis. Severe exacerbations are characterised by an ABG showing hypercapnia (PaCO<sub>2</sub> >6 kPa) and acidosis (pH <7.35).

## Patient and Public Involvement

Patients and the public were not involved in the design or conduct or reporting of the present research. Results were not disseminated to study participants.

## Statistical Analysis

Data are presented as means ± 1 S.D. for continuous variables (when applicable as median and interquartile range; IQR) and percentage for categorical variables. Normality was tested with the Kolmogorov–Smirnov test. For comparison between independent groups, the Student's *t*-test was used for normally distributed continuous variables and the Mann Whitney *U*-test for non-normally distributed continuous variables. Differences in categorical data were analysed by the Chi-square test and Fisher's exact test. The McNemar's test was used when comparing pairwise frequencies of categorical data. All analyses were undertaken using IBM SPSS Statistics, vs 27.0.0.0 (IBM SPSS, Chicago, IL, USA).

## Results

### Sample COPD: Descriptive Statistics

Table 1 summarises the descriptive statistics.

COPD patients with comorbid CHF were significantly older than COPD patients without comorbid CHF and were significantly younger than CHF patients. The group with all COPD patients was also significantly younger than the group with CHF patients. COPD patients with comorbid CHF presented significantly higher BMI and CCI scores than COPD patients without comorbid CHF did. The group with all COPD patients demonstrated significantly lower CCI than the group with CHF patients did. The groups with all COPD patients and COPD patients with comorbid CHF both demonstrated significantly lower SAT at inclusion than the CHF group did. COPD patients with comorbid CHF displayed significantly higher FEV<sub>1</sub>% predicted than COPD patients without comorbid CHF did. Never-smokers were significantly

**Table 1** Descriptive Statistics. Mean  $\pm$  I S.D. (Min-Max) if Not Otherwise Stated

Variables	COPD (All) (n = 43)				CHF (n = 41)	<sup>b</sup> p	<sup>c</sup> p
	All (n = 43)	COPD w/o CHF (n = 15)	COPD with CHF (n = 28)	<sup>a</sup> p			
Study participation (days) per patient; md (IQR)	323 (279)	362 (157)	201 (280)	0.228	358 (221)	0.140	0.374
Age (yrs)	76 $\pm$ 6 (65–88)	73 $\pm$ 5 (67–83)	78 $\pm$ 6 (65–88)	<b>0.015</b>	84 $\pm$ 7 (66–100)	<b>&lt;0.001</b>	<b>&lt;0.001</b>
Women; n (%)	25 (58)	10 (67)	15 (54)	0.4068	20 (49)	0.696	0.390
BMI (kg/m <sup>2</sup> )	24 $\pm$ 5 (13–41)	22 $\pm$ 6 (13–41)	25 $\pm$ 4 (17–34)	<b>0.029</b>	28 $\pm$ 5 (21–43)	0.083	0.903
CCI; md (IQR)	3 (4)	2 (2)	3 (3)	<b>0.007</b>	4 (3)	0.387	<b>0.048</b>
Current smokers; n (%)	11 (26)	5 (33)	6 (21)	0.394	0 (0)	n.a.	n.a.
Ex smokers; n (%)	29 (67)	10 (67)	19 (68)	0.937	19 (46)	0.238	0.196
Never smokers; n (%)	3 (7)	0 (0)	3 (11)	n.a.	22 (54)	<b>0.002</b>	<b>&lt;0.001</b>
SAT at base-line; md (IQR)	93 (5)	93 (3)	93 (6)	0.878	95 (4)	<b>0.005</b>	<b>&lt;0.001</b>
FEV <sub>1</sub> (% predicted)	39 $\pm$ 15 (15–74)	32 $\pm$ 10 (15–58)	43 $\pm$ 15 (20–74)	<b>0.020</b>	n.a.	n.a.	n.a.
GOLD stage 1; n (%)	0 (0)	0 (0)	0 (0)	n.a.	n.a.	n.a.	n.a.
GOLD stage 2; n (%)	9 (21)	1 (7)	8 (29)	n.a.	n.a.	n.a.	n.a.
GOLD stage 3; n (%)	21 (49)	9 (60)	12 (42)	0.284	n.a.	n.a.	n.a.
GOLD stage 4; n (%)	13 (30)	5 (33)	8 (29)	0.742	n.a.	n.a.	n.a.
GOLD group A; n (%)	0 (0)	0 (0)	0 (0)	n.a.	n.a.	n.a.	n.a.
GOLD group B; n (%)	2 (5)	0 (0)	2 (5)	n.a.	n.a.	n.a.	n.a.
GOLD group E; n (%)	41 (95)	15 (100)	26 (95)	0.289	n.a.	n.a.	n.a.
NYHA I; n (%)	0 (0)	n.a.	0 (0)	n.a.	0 (0)	n.a.	n.a.
NYHA II; n (%)	0 (0)	n.a.	0 (0)	n.a.	0 (0)	n.a.	n.a.
NYHA III; n (%)	22 (51)	n.a.	22 (79)	n.a.	31 (76)	<b>0.041</b>	n.a.
NYHA IV; n (%)	1 (2)	n.a.	1 (4) <sup>§</sup>	n.a.	10 (24)	0.080	n.a.
LVEF, preserved; n (%)	6 (14)	n.a.	6 (21)	n.a.	7 (17)	0.757	n.a.
LVEF, mid-range; n (%)	13 (30)	n.a.	13 (47)	n.a.	20 (49)	0.848	n.a.
LVEF, reduced; n (%)	9 (21)	n.a.	9 (32)	n.a.	14 (34)	0.862	n.a.
Number of exacerbations per patient; md (IQR)	2 (2)	3 (6)	1 (1)	<b>&lt;0.028</b>	0 (1)	<b>&lt;0.001</b>	<b>&lt;0.001</b>
ECOPDs; n (%)	107 (95)	61 (100)	46 (90)	0.012	n.a.	n.a.	n.a.
ECHFs; n (%)	5 (5)	n.a.	5 (10)	n.a.	18 (100)	n.a.	<b>&lt;0.001</b>

**Notes:** <sup>a</sup>p, p-value for the comparison COPD with CHF vs COPD w/o CHF. <sup>b</sup>p, p-value for the comparison COPD with CHF vs CHF. <sup>c</sup>p, p-value for the comparison COPD, all vs CHF. <sup>§</sup>Data on NYHA are missing for 5 subjects. p-values < 0.05 are indicated by bold figures.

**Abbreviations:** BMI, body mass index; CCI, Charlson Comorbidity Index; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; ECHF, exacerbation of chronic heart failure; ECOPD, exacerbation of chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; FEV<sub>1</sub> (% of predicted), forced expiratory volume in one second expressed as % of predicted; GOLD, global initiative for chronic obstructive lung disease; IQR, interquartile range; md, median; NYHA, New York Heart Association; SAT, blood oxygen saturation; S.D., standard deviation.

over-represented in the CHF group. In the COPD group with comorbid CHF, significantly more patients presented NYHA III than in the CHF group. CHF patients experienced significantly fewer exacerbations compared to COPD patients, and the frequency of ECHFs was significantly less compared to COPD patients with comorbid CHF.

## The Influence of CHF on ECOPD Severity (GOLD 2022 and 2023)

Table 2 shows the severity of all recorded ECOPDs among COPD patients without comorbid CHF (n = 61) and COPD patients with comorbid CHF (n = 46). The criteria of GOLD 2022 and GOLD 2023 were applied on the ECOPDs.

The GOLD 2023 criteria scored ECOPD severity less than GOLD 2022 did among COPD patients without comorbid CHF. This was observed by significantly more of mild ECOPDs and significantly less of severe ECOPDs. Notably, comorbid CHF had no significant influence on the distribution of ECOPDs mild, moderate and severe.

**Table 2** EOCOPD Severity Assessed by the Criteria of GOLD 2022 and GOLD 2023 (the Rome Proposal)

Severity	COPD w/o CHF, Exacerbations (n = 61)		COPD with CHF, Exacerbations (n = 46)		p-values			
	GOLD <sup>a</sup> 2022	GOLD <sup>a</sup> 2023	GOLD <sup>b</sup> 2022	GOLD <sup>b</sup> 2023	<sup>a</sup> 2022 vs <sup>a</sup> 2023	<sup>b</sup> 2022 vs <sup>b</sup> 2023	<sup>a</sup> 2022 vs <sup>b</sup> 2022	<sup>a</sup> 2023 vs <sup>b</sup> 2023
Mild exacerbations; n (%)	0 (0)	25 (41)	0 (0)	21 (46)	<b>&lt;0.001</b>	<b>&lt;0.001</b>	n.a.	0.629
Moderate exacerbations; n (%)	41 (67)	30 (49)	27 (55)	21 (46)	0.080	0.345	0.365	0.718
Severe exacerbations; n (%)	20 (33)	2 (3)	19 (45)	2 (4)	<b>&lt;0.001</b>	<b>&lt;0.001</b>	0.365	n.a.
Exacerbations with undefined severity; n (%)	0 (0)	4 (6)	0 (0)	2 (4)	n.a.	n.a.	n.a.	n.a.

**Notes:** p-values < 0.05 are indicated by bold figures. <sup>a</sup>2022 EOCOPD severity assessed by the criteria of GOLD 2022. Patient group COPD w/o CHF. <sup>a</sup>2023 EOCOPD severity assessed by the criteria of GOLD 2023. Patient group COPD w/o CHF. <sup>b</sup>2022 EOCOPD severity assessed by the criteria of GOLD 2022. Patient group COPD with CHF. <sup>b</sup>2023 EOCOPD severity assessed by the criteria of GOLD 2023. Patient group COPD with CHF.

**Abbreviations:** CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; EOCOPD, exacerbation of chronic obstructive pulmonary disease; GOLD, global initiative for chronic obstructive lung disease; n.a., not applicable.

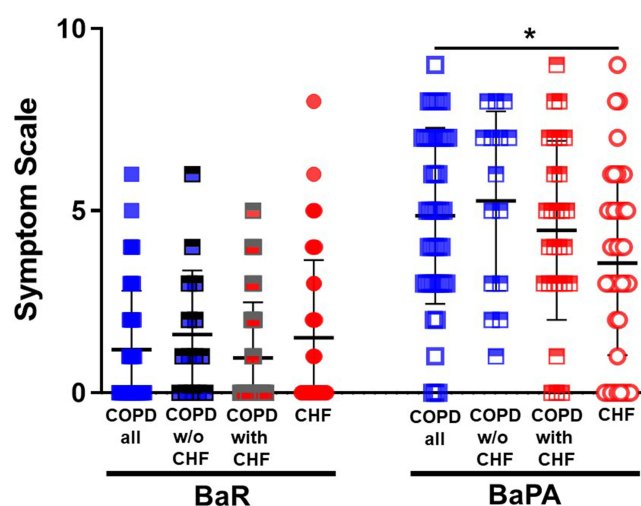
## Breathlessness at Inclusion

BaR and BaPA scores at inclusion (study day 1) are shown in Figure 1. The group with all COPD patients scored significantly ( $p < 0.05$ ) higher for BaPA than the CHF group did. No significant differences for BaR and BaPA were observed when COPD patients with comorbid CHF were compared with COPD patients without comorbid CHF and CHF patients. The number of patients scoring BaR from 0 to 3 in the four groups; all COPD patients, those without comorbid CHF, those with comorbid CHF and patients with CHF were 38 (88%), 13 (87%), 25 (89%) and 32 (78%), respectively.

## Breathlessness at the Peak of the Exacerbation

BaR and BaPA scores at exacerbation day 15 for all exacerbations observed in the groups studied are shown in Figure 2.

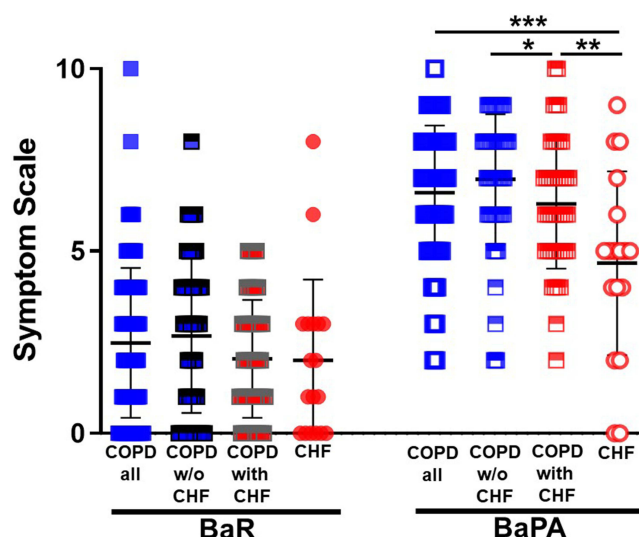
We found no significant differences between groups regarding BaR. The number of patients scoring BaR  $\geq 5$  in the four groups; all COPD patients, those without comorbid CHF, those with comorbid CHF and patients with CHF were 18



**Figure 1** BaR and BaPA at base-line study day 1 (at inclusion). The groups were all COPD patients (n = 43), two subgroups of COPD patients, that is those without comorbid CHF (n = 15) and those with comorbid CHF (n = 28), and CHF patients (n = 41). Mean values  $\pm$  S.D. are indicated. \* $p < 0.05$ .

**Abbreviations:** BaR, breathlessness at rest; BaPA, breathlessness at physical activity; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; S.D., standard deviation.





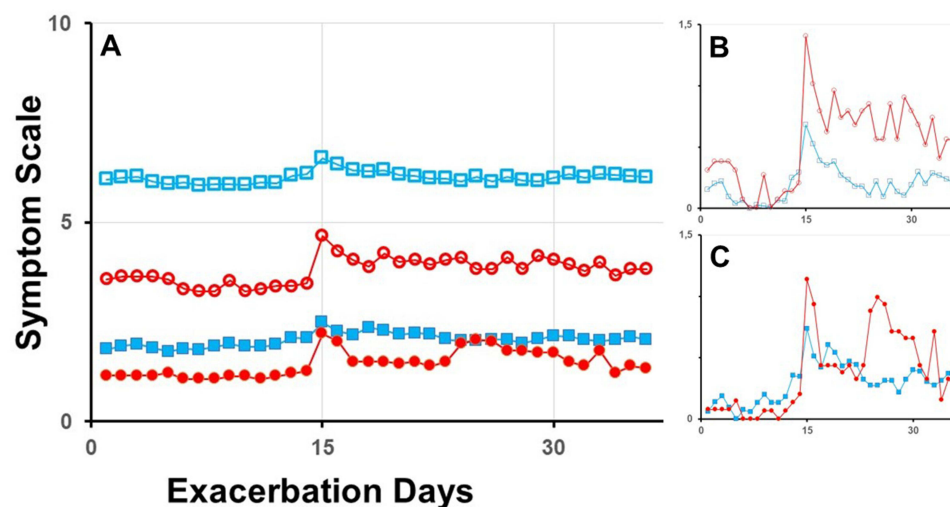
**Figure 2** BaR and BaPA at the peak of the exacerbations (day 15). The groups were the ECOPDs of all COPD patients ( $n = 107$ ), two subgroups of ECOPDs, that is those without comorbid CHF ( $n = 61$ ) and those with comorbid CHF ( $n = 46$ ), and the ECHFs of CHF patients ( $n = 18$ ). Mean values  $\pm$  S.D. are indicated. \* $p < 0.05$ ; \*\* $p < 0.01$ , \*\*\* $p < 0.001$ .

**Abbreviations:** BaR, breathlessness at rest; BaPA, breathlessness at physical activity; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; S.D., standard deviation.

(16%), 12 (20%), 6 (12%) and 2 (11%), respectively. For BaPA, we noticed a significantly lower scoring for ECOPDs of COPD patients with comorbid CHF compared to ECOPDs of COPD patients without comorbid CHF. The number of ECHFs was small ( $n = 18$ ), but the BaPA scoring for these exacerbations was significantly less than for ECOPDs in the group with all COPD patients and the group with COPD patients with comorbid CHF.

## Progression of Breathlessness During the Exacerbation

The progression of BaR and BaPA during the exacerbation is shown in Figure 3A–C (mean values are indicated by symbols). The diagnosis of the ECOPDs ( $n = 107$ ) in the group with all COPD patients ( $n = 43$ ) and the ECHFs ( $n = 18$ )



**Figure 3** (A) Mean values day-by-day during the exacerbation. Day 15 is the day when the exacerbation was diagnosed by HBHC staff and treatment with steroids and/or antibiotics (the ECOPDs) or diuretics (the ECHFs) was started. BaR (filled symbols) and BaPA (open symbols) during exacerbations among patients with COPD (all; blue squares and blue lines;  $n = 107$ ) and patients with CHF (red circles and red lines;  $n = 18$ ). (B and C) show the mean values adjusted to a shared baseline for BaPA (B) and BaR (C).

**Abbreviations:** BaR, breathlessness at rest; BaPA, breathlessness at physical activity; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; S.D., standard deviation.

in the group with CHF patients ( $n = 41$ ) was made at day 15, when treatment with steroids and/or antibiotics or diuretics was started. Progressions of BaR and BaPA, sharing the same baseline, are shown in [Figure 3B](#) and [C](#), respectively.

It became evident that the observed three-star significant difference for BaPA between the group with all COPD patients and the group with CHF in [Figure 2](#) was only an effect of a lower baseline for CHF patients compared to COPD patients. The same analysis performed on COPD patients without comorbid CHF and those with comorbid CHF gave similar results that the one-star difference in [Figure 2](#) depended on a lower baseline for COPD patients with comorbid CHF (data not shown).

## Discussion

The present study is the first of its kind. For the first time, the Rome proposal was applied on ECOPDs experienced by COPD patients with comorbid CHF, to understand whether comorbid CHF would have an impact on ECOPD severity assessment. As the Rome proposal includes the assessment of several vital signs of health, which may be influenced by comorbid CHF, one might think that comorbid CHF would have a significant influence on the assessment of ECOPD severity. Opposite to what may be expected, the present study shows that comorbid CHF did not interfere on ECOPD severity assessment, when the Rome proposal was applied. Nor did comorbid CHF significantly influence on BaR scoring. BaR scoring is a new and important parameter of ECOPD severity grading in the Rome proposal.

In the present study, the subjects studied were elderly, fragile patients with advanced stages of COPD and/or CHF. The data collected were analysed in two steps. Firstly, we demonstrated that the downgrading of ECOPD severity, observed when GOLD 2023 were compared with GOLD 2022, was due to the criteria applied ([Table 2](#)). Even in this population of patients with very advanced disease, the new guidelines almost eliminated severe exacerbations. This might make the new guidelines less useful in categorizing patients both clinically and in clinical trials. Comorbid CHF had no significant influence on the severity scoring ([Table 2](#)). Notably, scoring the severity according to the GOLD 2022 criteria resulted in approximately 20% severe ECOPDs, whether comorbid CHF was present or not, while GOLD 2023 criteria gave only a few % severe ECOPDs ([Table 2](#)). This observation may be explained by a recent study by Giezeman et al.<sup>27</sup> In that study, comorbid heart disease in patients with COPD was associated with an increased risk for all-cause hospitalisation and mortality, which was mainly due to an increase of hospitalisation and death of cardiovascular and other causes, but not because of respiratory disease.<sup>27</sup> Thus, the GOLD 2023 criteria is more specific on respiratory issues for the definition of severe ECOPD, limiting severe ECOPDs to those showing hypercapnia ( $\text{PaCO}_2 > 6 \text{ kPa}$ ) and acidosis ( $\text{pH} < 7.35$ ), that is, patients requiring hospitalisation due to the need of assisted ventilation and/or cautious surveillance.

Secondly, we analysed the influence of comorbid CHF on BaR scoring, experienced by patients at study inclusion ([Figure 1](#)) and during ECOPDs ([Figures 2](#) and [3](#)). The only published study we know of that applies the Rome proposal on ECOPDs is the one by Reumkens et al.<sup>28</sup> Since this study applies the Rome proposal on ECOPDs without any data on BaR, we thought it would be of particular interest to include an analysis of BaR in the present study. In these analyses, we observed no significant difference regarding BaR at study inclusion between COPD patients without CHF and those with comorbid CHF ([Figure 1](#)). Nor did CHF influence significantly on BaR when symptoms peaked at day 15 during the ECOPDs ([Figure 2](#)).

In the present study, breathlessness was also assessed at physical activity (BaPA) using a score from 0 to 10. This parameter is not included in the Rome proposal but may be of some value due to the additional information it provides on the health status. We observed a significant difference at inclusion when the group with all COPD patients was compared with CHF patients ([Figure 1](#)). The difference between these two groups regarding BaPA became even more significant at the peak of the breathlessness at day 15 during the exacerbations ([Figure 2](#)). The observed significance during the exacerbations was explained by a much lower baseline BaPA scoring among patients with CHF ([Figure 3](#)). This difference of baseline BaPA scoring may be due the pathogenesis behind. In COPD patients, breathlessness is mainly due to ventilatory constraints, while in patients with CHF breathlessness is mainly caused by an inadequate modulation of the cardiac output. In addition, COPD patients in the present study exhibited significantly less blood oxygenation than the CHF patients did ([Table 1](#)).

We also observed significantly lower BaPA scores among COPD patients with comorbid CHF compared to those without comorbid CHF (Figure 2). This observation on BaPA scoring may be compared with findings from a previous study, which employed the modified Medical Research Council (mMRC) questionnaire to score breathlessness.<sup>29</sup> This questionnaire scores breathlessness at varying degree of physical activity, as the minimum score 0 means that the patient is not troubled by breathlessness except on strenuous exercise, while the maximum score 4 means that the patient is too breathless to leave the house or breathless when dressing or undressing. In contrast to our study, Giezenman et al found that heart disease in general (not only CHF) contributed to lower health status and higher burden of breathlessness, scored with mMRC, in COPD patients.<sup>29</sup> A significantly higher FEV<sub>1</sub>% predicted among COPD patients with comorbid CHF in the present study might explain significantly lower BaPA scores (Table 1).

The Rome proposal states that the BaR values range from 0 to 3 in patients with COPD in a stable phase.<sup>15</sup> In the present study, 38 patients (88%) exhibited BaR values from 0 to 3 at inclusion in the group with all COPD patients. Corresponding figures for the two COPD subgroups, that is, COPD patients without comorbid CHF and those with comorbid CHF were 13 patients (87%) and 25 patients (89%). Hence, the BaR scoring >3 was not very frequent in the COPD patients studied. This observation suggests that the limit is set at a correct level, even when patients with great severity of the diseases causing the breathlessness are considered. Indeed, in the present study, all COPD patients presented with severe disease, that is, stage 3 or 4 disease (Table 1). Correspondingly, all CHF patients, including those with COPD and comorbid CHF, exhibited advanced disease, that is, NYHA III or IV. In addition, most patients with CHF displayed mid-range or reduced LVEF (Table 1).

The major limitations of the present study are a small sample size and a single centre study design. Moreover, our observations are restricted to the ECOPDs of the COPD phenotype presenting with advanced stages of COPD and frequent ECOPDs, with or without advanced CHF.

## Conclusion

In the present study, we find no evidence that comorbid CHF would interfere significantly with the parameters included in the Rome proposal (GOLD 2023).<sup>14,15</sup> We conclude that the Rome proposal can be safely applied even on COPD patients with very advanced comorbid CHF.

## Abbreviations

ABG, arterial blood gas; BMI, body mass index; BaR, breathlessness at rest; BaPA, breathlessness at physical activity; bpm, beats per minute; CAL, chronic airflow limitation; CAT, COPD Assessment Test; CCI, Charlson Comorbidity Index; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ECHF, exacerbation of chronic heart failure; ECOPD, exacerbation of COPD; ESC, European Society of Cardiology; FEV<sub>1</sub>, forced expiratory volume in one second; FEV<sub>1</sub> (% of predicted), forced expiratory volume in one second expressed as % of predicted; FVC, forced vital capacity; GOLD, global initiative for chronic obstructive lung disease; HBHC, hospital-based home care; HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HR, heart rate; IQR, interquartile range; LVEF, left ventricular ejection fraction; mMRC, modified Medical Research Council; n.a., not applicable; NYHA, New York Heart Association; RR, respiratory rate; SAT, blood oxygen saturation; S.D., standard deviation.

## Data Sharing Statement

The data upon which this analysis was based are available from Professor Hans Lennart Persson in anonymised form, upon receipt of a reasonable request. Contact details are Professor Hans Lennart Persson, Department of Respiratory Medicine in Linköping, Linköping University, SE-581 85 Linköping, Sweden. Email: lennart.persson@liu.se.

## Ethics Statement and Study Registration

The study was approved by the Swedish Ethical Review Authority (dnr: 2020-03308; L. Lind) according to the guidelines of the Declaration of Helsinki. All patients were included following verbal and written information of the study and after informed consent to participate. The study was registered at ISRCTN (ISRCTN34252610).



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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

PKJ reports honoraria for lectures from Chiesi. HLP reports honoraria for advisory boards/lectures from AstraZeneca, Boehringer Ingelheim, GlaxoSmithCline, Intermune, Roche and the Swedish Medical Products Agency. The authors report no other conflicts of interest in this work.

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