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ORIGINAL RESEARCH

Exploring Patterns of COPD Exacerbations and Comorbid Flare-Ups

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Background: Comorbidities are known to complicate disease management in patients with Chronic Obstructive Pulmonary Disease (COPD). This is partly due to lack of insight into the interplay of acute exacerbations of COPD (AECOPD) and comorbid flare-ups. This study aimed to explore patterns of AECOPDs and comorbid flare-ups.

Methods: Data of increased symptoms were extracted from a 12-month daily symptom follow-up database including patients with COPD and comorbidities (chronic heart failure (CHF), anxiety, depression) and transformed to visualizations of AECOPDs and comorbid flare-up patterns over time. Patterns were subsequently categorized using an inductive approach, based on both predominance (ie, which occurs most often) of AECOPDs or comorbid flare-ups, and their simultaneous (ie, simultaneous start in ≥ 50%) occurrence.

Results: We included 48 COPD patients (68 ± 9 years; comorbid CHF: 52%, anxiety: 40%, depression: 38%). In 25 patients with AECOPDs and CHF flare-ups, the following patterns were identified: AECOPDs predominant (n = 14), CHF flare-ups predominant (n = 5), AECOPDs nor CHF flare-ups predominant (n = 6). Of the 24 patients with AECOPDs and anxiety and/or depression flare-ups, anxiety and depression flare-ups occurred simultaneously in 15 patients. In 9 of these 24 patients, anxiety or depression flare-ups were observed independently from each other. In 31 of the included 48 patients, AECOPDs and comorbid flare-ups occurred mostly simultaneously.

Conclusion: Patients with COPD and common comorbidities show a variety of patterns of AECOPDs and comorbid flare-ups. Some patients, however, show repetitive patterns that could potentially be used to improve personalized disease management, if recognized.

Keywords: chronic obstructive pulmonary disease, heart failure, anxiety, depression, personalized medicine, disease monitoring

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a progressive lung disease, characterized by acute exacerbations (AECOPD): periods of suddenly worsened respiratory symptoms requiring additional medication or hospitalization.[1] COPD rarely is the only chronic disease a patient is suffering from. To illustrate, up to 68% of patients with COPD suffer from cardiovascular disease, up to 45% from anxiety and/or depression, and up to 20% from diabetes mellitus.[2] These comorbidities can severely complicate disease management in patients with COPD. Acute dyspnea, for example, can be a symptom of both an AECOPD and comorbid flare-ups, such as decompensation of chronic heart failure (CHF), or a panic attack.[3] Because symptoms are often not COPD-specific and may also indicate worsening of a comorbid disease, it is challenging to offer adequate acute treatment in these patients.[4,5]

Patients suffering from both COPD and CHF are at increased risk of AECOPDs compared to those with COPD without CHF because up to 26% of the AECOPDs are triggered by cardiovascular disease.[6] Both COPD and CHF may require hospitalization and are potentially life-threatening. To illustrate, one in five patients who decease shortly after AECOPD hospitalization die from a cardiovascular rather than respiratory cause.[7,8] Moreover, about 8 to 45% of COPD

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patients suffer from mental health disease,[2,9] further increasing the disease burden.[1] Also the presence of anxiety and depression increases the risk of AECOPDs, for example by impairing the immune system, reducing medication adherence, and worsening (the perception of) acute symptoms leading to seeking early medical attention.[10–12] Not only can mental health diseases impact the course of COPD, but vice versa, COPD may also contribute to anxiety and depression severity.[11,13] Pathophysiological pathways for anxiety and depression in COPD are not yet fully understood, but include factors such as smoking, systemic inflammation, and hypoxia.[11,13]

Although plausible pathophysiological pathways of interaction between COPD and comorbidities have been explored, a lack of knowledge persists into the interplay of AECOPDs and comorbid flare-ups.[5,6,11,14,15] In this paper, we aimed to explore multimorbid disease patterns in COPD patients with comorbidities (ie, CHF, anxiety, depression) through visualization of AECOPDs and comorbid flare-ups by means of a secondary analysis using daily symptom data. Visualizing multimorbid patient patterns from daily symptom data is novel and could contribute to personalized disease management by improving the recognition of AECOPD and flare-up patterns. It could thereby facilitate faster and optimal treatment actions in patients with multimorbidity.

Materials and Methods

Study Design & Population

A randomized controlled trial (COPE-III study) was conducted from 2012 to 2016 in two hospitals in the Netherlands and three in South Australia.[16,17] The COPE-III study was designed in accordance with the Declaration of Helsinki and was approved by the Medical Ethical Committee Twente (NL39516.044.12) and the Southern Adelaide Clinical Human Research Ethics Committee (37-12). Participants' written informed consent was obtained prior to data collection. For inclusion in the COPE-III study, patients needed to have a clinical diagnosis of COPD GOLD stage II–IV[1] and at least one comorbidity (ie, CHF, ischemic heart disease (IHD), symptomatic anxiety/depression, diabetes). Detailed in- and exclusion criteria are described in the COPE-III protocol.[16] The COPE-III study investigated the effectiveness of a self-management exacerbation action plan. For this purpose, patients kept a multimorbid symptom diary during a 12-month follow-up.[5] Each day, patients were asked whether their symptoms in the last 24 hours (eg, sputum color for COPD, sudden weight gain for CHF) were not, slightly, or significantly increased compared to usual (ie, symptoms they experience during stable phase). An overview of the diary including all symptoms can be retrieved from the online supplement of the COPE-III study.[17] All patients received training on how to fill in their daily symptom diaries.

For the current analysis, we only used the symptom data of COPE-III patients who had: 1) comorbid CHF (ie, symptoms and signs typical of heart failure and objective evidence of a structural or functional abnormality of the heart at rest),[18] and/or comorbid anxiety (ie, ≥ 11 Hospital Anxiety and Depression Scale (HADS), anxiety domain[19] and/or having anxiety symptoms that are being treated) and/or comorbid depression (ie, ≥ 11 HADS, depression domain[19] and/or having depression symptoms that are being treated); and 2) at least one AECOPD and at least one flare-up of CHF, anxiety, and/or depression during the one-year follow-up period. COPE-III patients with only comorbid IHD and/or diabetes were, thus, excluded.

Definitions

Based on the change in daily symptoms, AECOPDs and comorbid flare-ups were identified and extracted from the daily symptom diaries. Definitions detailing the start and end of AECOPDs and comorbid flare-ups are described in Table 1.

Data Processing and Analysis

The data processing (including visualizations) and statistical analyses were conducted with the statistical software R version 4.2.2. Patient baseline data and follow-up data (eg, number of (respiratory-related) hospitalizations, deaths) were analyzed by computing the mean with standard deviation for parametric continuous data, the median with interquartile range in case of non-parametric continuous data, or numbers and percentages in case of discrete data. Exacerbation and flare-up rates were calculated as per person-year (ie, total number of days patients participated in the COPE-III study divided by 365 days). Daily symptom data were used to identify the start and end of AECOPDs and flare-ups of CHF, anxiety, and depression. The per-

Table 1 Definitions of COPD Exacerbations and Comorbid Flare-Ups[a]

	COPD	CHF	Anxiety	Depression
Start of an exacerbation/ flare-up	A clear negative change in two major symptoms (ie, dyspnea, sputum production, sputum color) or one major and one minor symptom (ie, cough, wheeze, and fever (> 38.5°C)) for two consecutive days[20,21]	The first day with a clear negative change in at least one symptom (ie, overnight weight increase > 1 kg, swelling of ankles or abdomen, wake up at night short of breath) from baseline, for at least two consecutive days	The first day with a clear negative change in feelings of anxiety from baseline, for at least five consecutive days	The first day with a clear negative change in depressive feelings from baseline, for at least five consecutive days
End of an exacerbation/ flare-up	The first day of 1) three successive days that the patient has returned to his normal health state or 2) seven consecutive days on which the patient continuously reports no or only a slight increase in symptoms compared to baseline, with no fever or change in sputum color	The first day of: 1) three consecutive successive days that the patient has returned to his normal baseline cardiac health state; 2) seven consecutive days on which patients continuously reported no or only a slightly increase of CHF symptoms compared to baseline	The first day of: 1) five consecutive successive days that the patient has returned to his normal baseline anxiety health state; 2) seven consecutive days on which patients continuously reported no or only a slightly increase in anxiety compared to baseline	The first day of: 1) five consecutive successive days that the patient has returned to his normal baseline depression health state; 2) seven consecutive days on which patients continuously reported no or only a slightly increase of depressive feelings compared to baseline

Note: [a]These definitions have also been used in the COPE-III study.[16,17]
Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; CHF, Chronic Heart Failure.

patient visualizations of AECOPDs and comorbid flare-ups during one year of follow-up were subsequently computed on a timeline following the definitions described in Table 1. Based on the change in daily symptoms, AECOPDs and comorbid flare-ups were identified, starting from the day of inclusion (day 1).

Given the explorative aim of our study, a so-called "inductive" categorization approach was taken, as this approach is considered most appropriate in exploratory, qualitative research to describe the results at a group level.[22] After visualizing all patient patterns over time, these were studied by three authors (SvD, MBK, AL). Based on all patterns observed, the three authors independently drafted a flowchart to categorize all patterns based on: 1a) predominance of either AECOPDs or comorbid CHF flare-ups (ie, which is most frequently (≥ 50%) observed), or 1b) simultaneous occurrence of flare-ups of anxiety and depression (ie, whether they most frequently (≥ 50%) start simultaneously), and 2) simultaneous occurrence of AECOPD and comorbid flare-ups of CHF, anxiety or depression. The three flowchart drafts were then used to decide on a final flowchart (Figure 1) by means of a discussion between the three authors. In the next step, the authors independently assigned all observed patterns to categories using the final flowchart. If there were discrepancies between the authors, the final decision regarding the category assignment was made through discussion.

Results

The patient inclusion for the current analyses is presented in Figure 2. Out of the 201 COPE-III patients,[17] 92 patients had at least one AECOPD or one comorbid flare-up. Two of these patients had extreme long AECOPDs (>300 days) and were excluded from further analyses. A further 42 patients were excluded, because they had only AECOPDs (n = 40) or experienced only one flare-up of CHF (n = 1) or depression (n = 1) during the one-year follow-up. Baseline characteristics of the 48 included patients are detailed in Table 2. The mean age was 68.2 years and 60.4% were male. There were 25 (52.1%) patients with COPD and comorbid CHF, 19 (39.6%) with anxiety, and 18 (37.5%) with depression. The comorbidities and their co-existence at baseline are shown in Figure 3.

From the 48 included patients, 37 completed follow-up, 5 patients died, and 6 patients were lost to follow-up (too heavily deteriorated health (n = 2), lung cancer (n = 1), palliative care for terminal CHF (n = 1), other reason (n = 2)). An

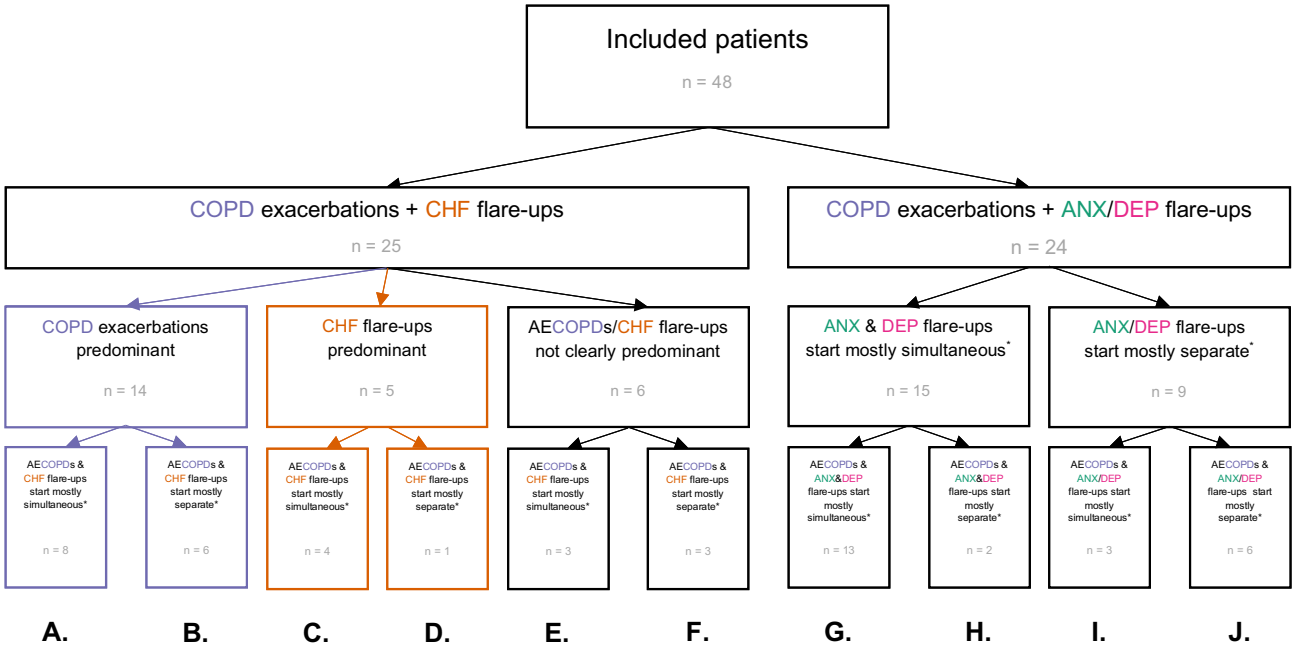

Figure 1 Flowchart reflecting patient inclusion and the categorization of AECOPD and comorbid flare-up patterns over one year follow-up*.
Notes: *Mostly simultaneous means ≥ 50%; mostly separate means < 50%.
Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; DM, Diabetes Mellitus; CHF, Chronic Heart Failure; ANX, anxiety; DEP, depression.

average of 5.3 AECOPDs, 4.3 CHF flare-ups, 2.0 anxiety flare-ups, and 1.7 depression flare-ups were observed per person-year. A summary of the follow-up information of all included patients is provided in Table 3.

Figure 1 displays the flowchart with which patient follow-up visualizations were categorized. Eventually, patients were divided over ten sub-categories (Figure 1). Twenty-five of the 48 patients (52%) experienced both AECOPD and flare-ups of CHF during follow-up. A combination of AECOPDs and flare-ups of anxiety and/or depression was observed in 24 patients (50%). Figure 4 presents patient pattern examples for each of the ten defined sub-categories. All 48 visualized patient patterns are presented in the e-Appendix. One patient was assigned to two categories as this patient had two AECOPDs that both started simultaneously with flare-ups of CHF, anxiety, and depression (Figure 4K).

AECOPDs and Flare-Ups of CHF

In the 25 patients who experienced both AECOPDs and CHF flare-ups (Figure 1, bottom left), AECOPDs were more frequently present than CHF flare-ups (ie, AECOPDs were predominant over CHF flare-ups) in 14 patients (56%). In this subgroup of 14 patients, CHF flare-ups occurred simultaneously with AECOPDs in eight patients (Figure 4A), and separately from AECOPDs in six (Figure 4B). In patients in whom CHF flare-ups were predominant (n = 5; 20%), CHF flare-ups occurred simultaneously with AECOPDs in four patients (Figure 4C), and separately from AECOPDs in one (Figure 4D). In patients with no AECOPD or CHF flare-up predominance (n = 6; 24%), AECOPDs and CHF flare-ups occurred simultaneously in three patients (Figure 4E) and separately in three patients (Figure 4F).

AECOPDs and Flare-Ups of Anxiety and/or Depression

In the 24 patients with both AECOPDs and flare-ups of anxiety and/or depression (Figure 1), the majority of the flare-ups of anxiety and depression occurred simultaneously (15 patients; 63%). In 13 of these 15 patients, anxiety and depression flare-ups started simultaneously with AECOPDs (Figure 4G), and separately from AECOPDs in two patients (Figure 4H). From those in whom flare-ups of anxiety and depression started separately from each other (n = 9; 38%), one of these flare-ups started simultaneously with AECOPDs in three patients (Figure 4I) and at different points in time from AECOPDs in six patients (Figure 4J).

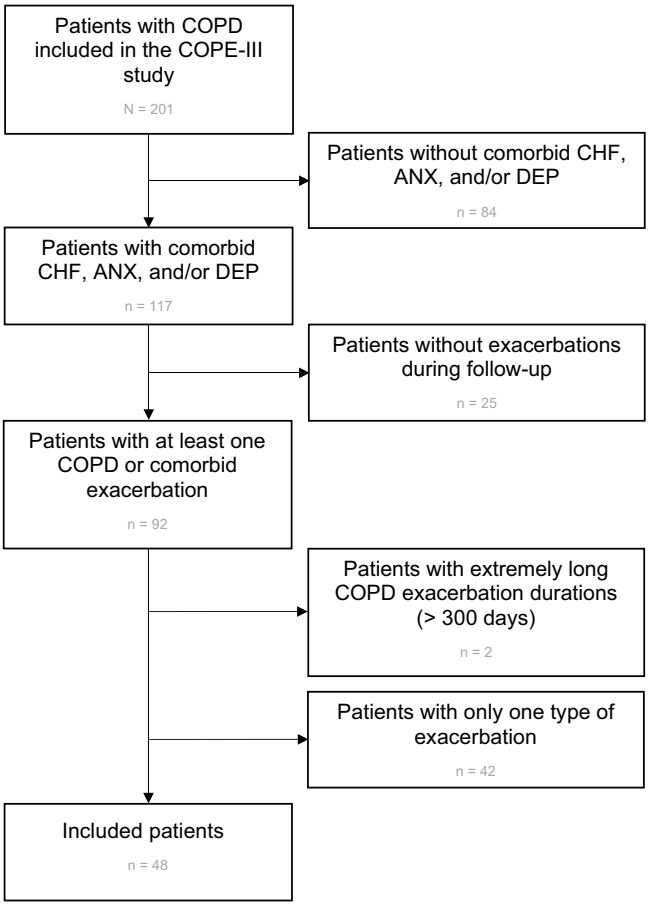

Figure 2 Flowchart reflecting the patient inclusion from the original COPE-III study for our analysis.
Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; CHF, Chronic Heart Failure; ANX, anxiety; DEP, depression.

Discussion

In this study, patients' AECOPD and comorbid flare-up patterns were explored by means of visualizations using patient-reported daily symptom data. A large variety in multimorbid patterns was observed across patients. In patients with COPD and comorbidities, AECOPDs and comorbid flare-ups regularly occur simultaneously, but certainly not always. These insights will probably be recognized by many caregivers from daily practice, where an AECOPD will or will not be accompanied by decompensated CHF[23] or episodes of worsened anxiety and/or depression.[24–26]

In patients with both AECOPDs and CHF flare-ups, we identified patients in whom either AECOPDs or flare-ups of CHF were predominantly present during follow-up, as well as patients in whom neither of the two were predominantly present. Differences in severity between the two diseases may explain these differences in predominance, given that more severe COPD or CHF increase the risk of AECOPDs[27] or decompensated CHF,[28,29] respectively. In the majority of patients who showed patterns containing both AECOPDs and CHF flare-ups, these occurred repeatedly simultaneously. Several pathophysiological mechanisms underlying this interplay are known.[6] For example, due to CHF, oxygen transport becomes inefficient as congestion builds up in the lungs, causing and/or intensifying acute COPD symptoms.[6] Vice versa, an AECOPD may trigger decompensated CHF: respiratory infections, often underlying an AECOPD, are also associated with decompensated CHF in 10 to 16% of the hospital admissions.[30] Furthermore, AECOPD increases the airflow obstruction, causing hypercapnia potentially leading to oxygen insufficiency for the heart.[14,31] Several researchers, therefore, speak of a cardiopulmonary continuum rather than of COPD and CHF as two separate diseases.[31,32] Our observation that many patients having simultaneous AECOPDs and CHF flare-ups, seems to

Table 2 Baseline Characteristics of 48 Included Patients with COPD

Characteristic at Baseline	**N = 48**
Age (years)	68.2 ± 9.2
Male sex	29 (60.4)
Comorbid chronic heart failure	25 (52.1)
Comorbid anxiety	19 (39.6)
Comorbid depression	18 (37.5)
Comorbid ischemic heart disease	19 (39.6)
Comorbid diabetes mellitus	18 (37.5)
Current smoker	10 (20.8)
COPD exacerbations 2 years prior to inclusion[a]	3 [1–5]
Hospitalizations 1 year prior to inclusion	1 [1–1]
Smoking history (pack-years)[a]	43.6 ± 23.8
Body mass index (kg/m^2)	30.9 ± 7.3
Dyspnea score (mMRC)	2.6 ± 0.9
Post-bronchodilator spirometry	
FEV_1 (L)	1.3 ± 0.5
FEV_1% predicted	48.7 ± 15.5
FEV_1/FVC ratio	49.8 ± 14.7
2007 GOLD COPD classification	
II	24 (50.0)
III	19 (39.6)
IV	5 (10.4)
BODE score[b]	4.4 ± 2.2
6-minute walking distance (m)[b]	274.9 ± 115.1

Notes: Data are presented as N (%), mean ± standard deviation or median [interquartile range]. [a]2 missing values. [b]3 missing values.

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; FEV_1, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; BODE, Body mass index, Obstruction, Dyspnea, and Exercise.

be in line with this statement. In some patients, however, AECOPDs seem not to relate to CHF flare-ups, indicating that distinct mechanisms may be driving deterioration of COPD or CHF in some patients.

Notably, flare-ups of anxiety and depression most frequently occurred together in our study. This is in line with research showing that symptoms of anxiety and depression do not emerge isolated very often.[33,34] Flare-ups of anxiety and depression were mainly observed simultaneously with AECOPDs. Although pathways of increased symptoms of mental diseases and COPD are not yet fully understood, three mechanisms could explain this simultaneous occurrence. First, AECOPDs reduce the patients' sense of control of their health and, consequently, increase symptoms of anxiety and/or depression.[12] Second, patients with anxiety and/or depression may have a worsened perception of acute

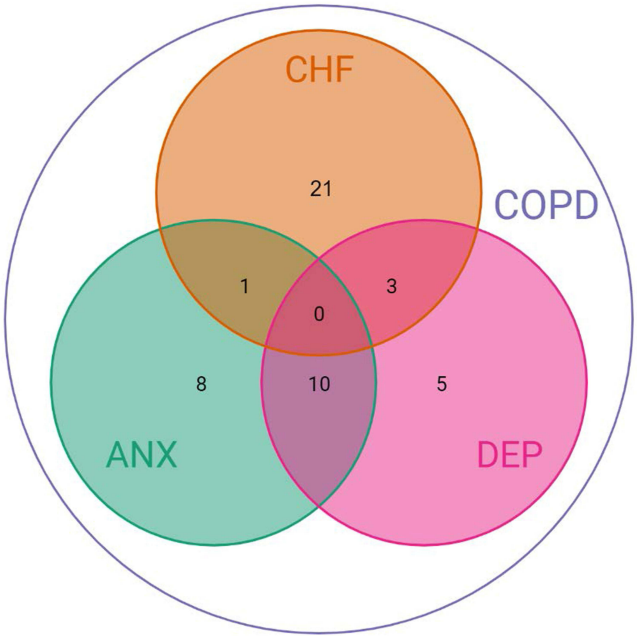

Figure 3 Venn diagram showing numbers of patients according to baseline (combinations of) comorbidities (N = 48).
Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; CHF: Chronic Heart Failure; ANX: anxiety; DEP: depression.

symptoms, given that their physiological parameters are less severe when hospitalized compared with patients without comorbid anxiety or depression.[11] They may, therefore, be more prone to being hospitalized for less severe or misdiagnosed AECOPDs.[11] Regardless of perception, anxiety and depression can also contribute to actual increased dyspnea.[12] Third, symptomatic depression may directly impair the immune system, which increases the risk of respiratory infections and, consequently, AECOPDs.[10,11] Since patients with comorbid mental diseases recover relatively slowly after an AECOPD,[26] addressing mental health issues when offering acute support is important in addition to treatment of AECOPD.[25,35]

The wide variety of patterns observed in this study argue for personalized, but more importantly multidisciplinary, disease management in COPD patients with multimorbidity. For instance, if within-patient patterns were recognized in usual clinical practice, these could be communicated to patients. Providing feedback about the disease trajectory would empower patients in timely recognizing their need for care by increased symptoms and taking appropriate action (eg, contact caregiver, self-treatment, relaxation exercises).[36] Furthermore, by sharing multimorbid disease patterns, patients could gain more insight into their multimorbid disease, which may improve medication adherence, prevent hospital admissions, and ultimately benefit the patient's health.[36]

A "one size fits all" care plan is certainly inappropriate, as our results have confirmed once again that "no single person-centered care plan could or should be the same".[37] It is about time that multidisciplinary approaches will actually be used for these patients, something that is already advised,[2,3] but rarely implemented in clinical practice.[38] For instance, the fact that departments of pulmonology and cardiology often function as two separate disciplines is not in line with the fact that the lungs and heart are inseparable. Whereas it will require additional effort from clinicians to work beyond the boundaries of one's own discipline, ignoring the cardiopulmonary interplay is costly, for the patient's health as well as for societal economic burden.[39]

Our study has several strengths. First and foremost, our study is unique in visualizing patterns of AECOPDs and comorbid flare-ups based on daily patient-reported symptom data. These can be generalized to the large group of patients with COPD with comorbidities and are typically treated in practice. Second, the categorization of individual patient patterns into ten categories has been conducted by three independent researchers in a systematic and robust way. An inductive approach was chosen (ie, the categories were derived from the patterns observed), which is considered most suitable for exploratory purposes.[22] Third, the symptom diaries were designed to minimize recall bias: symptoms were

Table 3 Exacerbations of COPD, Comorbid Flare-Ups, Hospitalizations and Deaths and Their Rates per Person-Year[a] During Follow-Up

Disease Events	N = 48
COPD exacerbations	
Median [IQR]	3 [2–8]
Rate (per person-year)	5.3
CHF flare-ups[b]	
Median [IQR]	2 [1–4]
Rate (per person-year)	4.3
Anxiety flare-ups[c]	
Median [IQR]	1 [1–2]
Rate (per person-year)	2.0
Depression flare-ups[c]	
Median [IQR]	1 [1–2]
Rate (per person-year)	1.7
All-cause hospitalizations	
Rate (per person-year)	1.8
Respiratory-related hospitalizations	
Rate (per person-year)	1.2
Deaths	
Rate (per person-year)	0.1

Notes: [a]A person-year was calculated as the number of total days study participants were followed divided by 365 days. [b]CHF flare-up rates were calculated using the person-years for patients who were diagnosed with CHF at baseline (n = 25). [c]Anxiety and depression flare-up rates were calculated using the person-years for patients who were diagnosed with anxiety and/or depression at baseline (n = 24).

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; CHF, Chronic Heart Failure; IQR, inter-quartile range.

prospectively and daily collected, extra information was only asked if symptoms had worsened, and patients were extensively trained in keeping the diary.[40] In addition, the COPD exacerbations and comorbid flare-ups were defined based on a combination of symptoms,[17] which gives detailed day-to-day information compared to a definition based on pharmacologic treatment only. Fourth, 37 of 48 included patients completed the one-year follow-up, resulting in a mean follow-up of 302 days, reflecting a high compliance rate (82.7%) comparable to the original COPE-III study.[17] Finally, using diaries instead of face-to-face symptom reporting, may have given a feeling of safety to report mental health symptoms, whereas the possibility that anxiety is underlying to increased dyspnea is likely frequently ignored in the clinic because respiratory symptoms are often attributed to an AECOPD only.[25]

Our study also has several limitations. First, next to CHF, anxiety, and depression, we could have taken other comorbidities into account, such as IHD, of which symptoms were collected during the COPE-III study. However, an increase in at least one of the IHD symptoms was defined as an event, lasting only one day, rather than as a longer period of time with an on- and offset. Combined with the fact that these events were defined based on unspecific symptoms,

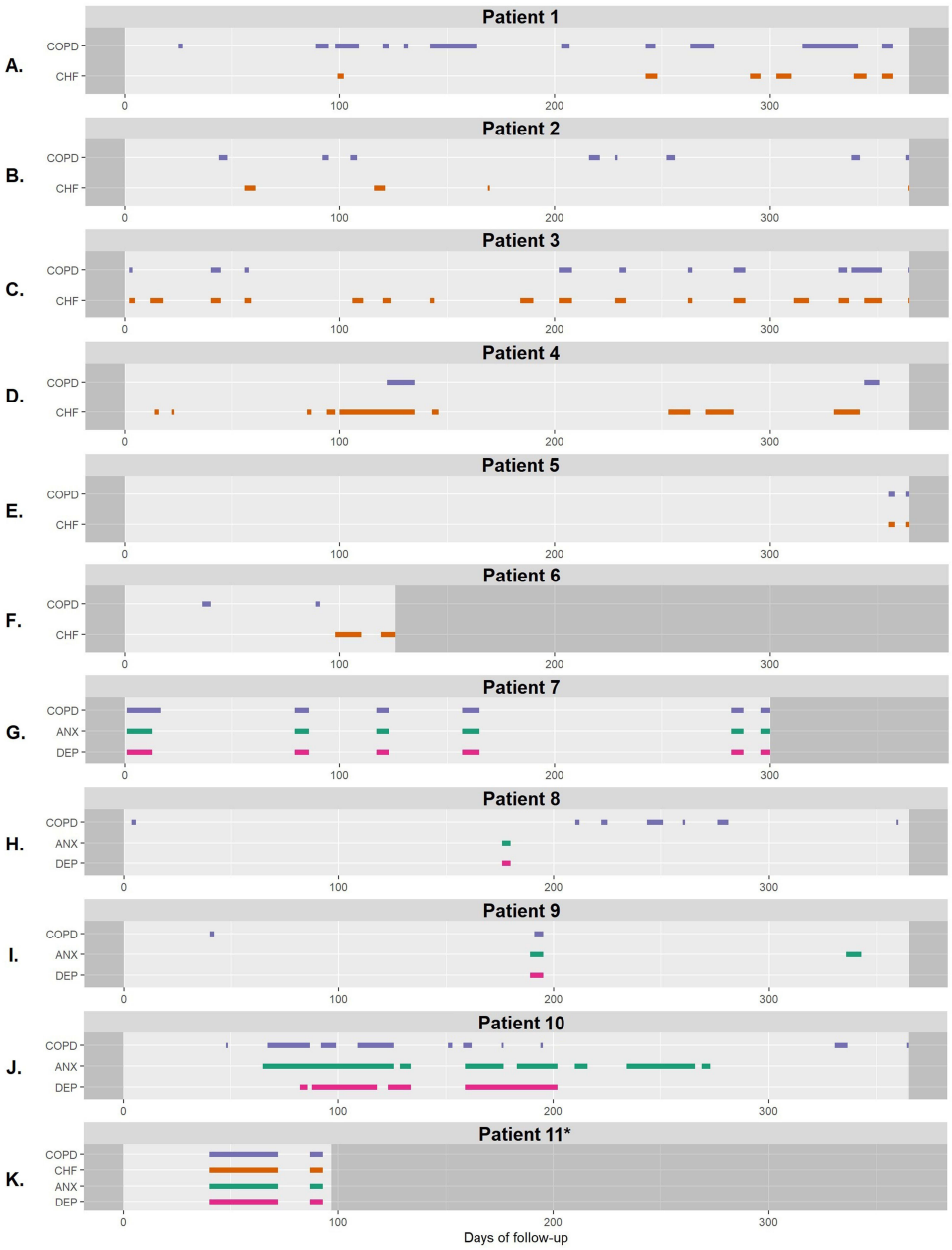

Figure 4 Examples of 11 patterns of acute exacerbations of COPD and comorbid flare-ups. (**A**) COPD exacerbations predominant – AECOPDs & CHF flare-ups start mostly simultaneous; (**B**) COPD exacerbations predominant – AECOPDs & CHF flare-ups start mostly separate; (**C**) CHF flare-ups predominant – AECOPDs & CHF flare-ups start mostly simultaneous; (**D**) CHF flare-ups predominant – AECOPDs & CHF flare-ups start mostly separate; (**E**) AECOPDs/CHF flare-ups not clearly predominant – AECOPDs & CHF flare-ups start mostly simultaneous; (**F**) AECOPDs/CHF flare-ups not clearly predominant – AECOPDs & CHF flare-ups start mostly separate; (**G**) ANX & DEP flare-ups start mostly simultaneous – AECOPDs & ANX&DEP flare-ups start mostly simultaneous; (**H**) ANX & DEP flare-ups start mostly simultaneous – AECOPDs & ANX&DEP flare-ups start mostly separate; (**I**) ANX/DEP flare-ups start mostly separate – AECOPDs & ANX&DEP flare-ups start mostly simultaneous; (**J**) ANX/DEP flare-ups start mostly separate – AECOPDs & ANX&DEP flare-ups start mostly separate; (**K**) Due to the presence of AECOPD and flare-ups of CHF, ANX and DEP, patient 11 (**K**) was assigned to two groups: 1) "COPD exacerbations + CHF flare-ups – AECOPDs/CHF flare-ups not clearly predominant – AECOPDs & CHF flare-ups start mostly simultaneous" (Figure 1C), 2) "COPD exacerbations + ANX/DEP flare-ups – ANX & DEP flare-ups start mostly simultaneous – AECOPDs & ANX&DEP flare-ups start mostly simultaneous" (Figure 1G).

Note:

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; CHF, Chronic Heart Failure; ANX, anxiety; DEP, depression; AECOPD, Acute Exacerbation of COPD.

justifiably interpreting IHD events in our study would have been difficult. Second, the fact that comorbid flare-ups are difficult to differentiate from AECOPDs based on increased symptoms,[4,30] potentially meant that patients had difficulty reporting disease-specific symptoms, which may have influenced our data. Nonetheless, in patients who show AECOPDs and comorbid flare-ups, these certainly do not always occur simultaneously, as shown by our results. Thus, to a considerable extent, distinct AECOPDs and comorbid flare-ups could be identified based on symptoms reported by patients when properly trained in completing daily symptoms diaries (ie, at least two sessions including coaching on how to recognize and differentiate increased symptoms compared to stable state[16]). Third, whereas we advocate for personalized and multidisciplinary care, our categorization was partly based on distinct disease domains. However, the derived categories should not be seen as the main results of the study, but rather as a tool to summarize this study's results in order to draw conclusions on a group-level.

Our study provides novel insights into the interplay of AECOPDs and comorbid flare-ups, but future research should validate our findings. A considerable addition would be to look at consistent repetition of patterns within patients over a longer period of follow-up, after which treatment approaches could be developed taking these patterns into account. What such a new treatment approach should include and how AECOPD and comorbid flare-up pattern visualizations can be of additional value would be an important research question. Another essential next step would be to investigate the interplay of COPD with comorbidities in terms of timing: what comes first, and potentially triggers the other? Also, are daily symptom diaries sensitive enough to measure this, or should alternative measures be considered? It has become clear from our results that AECOPDs frequently occur simultaneously with comorbid flare-ups, so pathophysiological mechanisms underlying this interplay also require further research.

Conclusion

This study revealed that patients with COPD and common comorbidities show a variety of AECOPD and comorbid flare-up patterns. If repetitive within-patient patterns of AECOPD and comorbid flare-ups would be recognized in clinical practice, personalized and multidisciplinary disease management could be optimized, which could ultimately lead to improved health outcomes. Future research should focus on validating these patterns in patients with multimorbidity over a longer period of follow-up.

Abbreviations

AECOPD, Acute Exacerbation of Chronic Obstructive Pulmonary Disease; CHF, Chronic Heart Failure; COPD, Chronic Obstructive Pulmonary Disease; HADS, Hospital Anxiety and Depression Scale; IHD, Ischemic Heart Disease.

Data Sharing Statement

Individual multimorbid patterns are shared in this paper's Supplementary Table 1. Detailed deidentified patient data are stored in archived datasets for a total of 15 years and can be requested from the corresponding author Anke Lenferink. The R coding used to visualize the patterns can also be requested from the corresponding author.

Ethics Approval

This study was approved by the Medical Ethical Committee Twente and the Flinders Southern Adelaide Clinical Human Research Ethics Committee, and was registered in the public Australian New Zealand Clinical Trials Registry (ACTRN12612000514808).

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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; drafted, revised or critically reviewed the article; gave approval of the final 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

The authors report no conflicts of interest in this work.

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