Clusters of Comorbidities Based on Validated Objective Measurements and Systemic Inflammation in Patients with Chronic Obstructive Pulmonary Disease

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Rationale: Comorbidities contribute to disease severity and mortality in patients with chronic obstructive pulmonary disease (COPD). Comorbidities have been studied individually and were mostly based on self-reports. The coexistence of objectively identified comorbidities and the role of low-grade systemic inflammation in the pathophysiology of COPD remain to be elucidated.

Objectives: To cluster 13 clinically important objectively identified comorbidities, and to characterize the comorbidity clusters in terms of clinical outcomes and systemic inflammation.

Methods: A total of 213 patients with COPD (FEV1 5 17% predicted; men, 59%; age, 64 ± 7 yr) were included prospectively. Comorbidities were based on well-known cut-offs identified in the peer-reviewed English literature. Systemic inflammatory biomarkers were determined in all patients. Self-organizing maps were used to generate comorbidity clusters.

Measurements and Main Results: A total of 97.7% of all patients had one or more comorbidities and 53.5% had four or more comorbidities. Five comorbidity clusters were identified: (1) less comorbidity, (2) cardiovascular, (3) cachectic, (4) metabolic, and (5) psychological. Comorbidity clusters differed in health status and were comparable with respect to disease severity. An increased inflammatory state was observed only for tumor necrosis factor (TNF) receptors in the metabolic cluster (geometric mean [lower and upper limit]; TNF-R1, 2,377 [1,850, 3,055] pg/ml, confidence, 98.5%; TNF-R2, 4,080 [3,115, 5,344] pg/ml, confidence, 98.8%) and only for IL-6 in the cardiovascular cluster (IL-6, 3.4 [1.8, 6.6] pg/ml; confidence, 99.8%).

Conclusions: Multimorbidity is common in patients with COPD, and different comorbidity clusters can be identified. Low-grade systemic inflammation is mostly comparable among comorbidity clusters. Increasing knowledge on the interactions between comorbidities increases the understanding of their development and contributes to strategies for prevention or improved treatment.

Keywords: chronic obstructive pulmonary disease; comorbidity; cluster analysis; systemic inflammation

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What This Study Adds to the Field

This study evaluated 13 comorbidities based on validated objective measurements and illustrated the high prevalence of multimorbidity in patients with COPD. Five distinct comorbidity clusters were identified using a nonparametric regression technique. Although disease severity was comparable among comorbidity clusters, it was markedly different in terms of health status. Mostly, systemic inflammatory markers were comparable among the clusters. This study expands the understanding of the cooccurrence of chronic conditions in patients with COPD and sheds new light on the possible cause and pathophysiologic role of systemic inflammation in COPD.

Chronic obstructive pulmonary disease (COPD) is a major global health concern, causing considerable morbidity and mortality around the world. Although defined by the presence of chronic airflow limitation, COPD is nowadays considered a complex, heterogeneous, and multicomponent condition (1). It is increasingly recognized that the presence of other chronic conditions (comorbidities), such as cardiovascular disease, depression, osteoporosis, anemia, and diabetes, substantially contributes to the severity of the disease (2). Comorbidities not only affect symptom burden, functional performance, and health status in patients with COPD (3), but also the risk of hospitalization (4) and mortality (4, 5).

To date, most studies on the impact of comorbidities in COPD used data on self-reported concurrent chronic conditions. This may limit the internal validity of these studies (4–13). Indeed, self-reported data are most probably underestimating the true prevalence of comorbidities in COPD (14). Moreover, most comorbidities have been studied separately, whereas most elderly have two or more chronic morbidities (15). Overlap in self-reported comorbidities has been shown in primary care patients with COPD (11). Although some associations among objectively identified comorbidities, such as vascular stiffness
and osteoporosis (16), have been studied, it is currently unknown whether and to what extent comorbidities cluster in COPD. Also, it remains unclear whether or not patients with different comorbidity profiles differ in disease severity, pharmacologic treatment, or other relevant clinical outcomes.

Persistent low-grade systemic inflammation may be the link between COPD and comorbidities (17). Simultaneously elevated inflammatory markers have been associated with an increased risk of comorbidities (18). However, the ECLIPSE study reported that chronic systemic inflammation is a feature in only a small proportion of the patients with COPD (19). Intriguingly, the risk of chronic systemic inflammation was not increased in patients with self-reported cardiovascular comorbidity, whereas older age and obese body mass index (BMI), among other factors, were associated with this feature. These observations shed new light on the role of chronic inflammation in the development of comorbidities in COPD and on the possible cause of systemic inflammation in COPD.

Therefore, the present study investigated the frequency of 13 clinically relevant and objectively identified comorbidities and the clustering of these comorbidities in a well-characterized cohort of patients with COPD. In addition, potential differences in disease severity and clinical characteristics, inflammatory status, and current pharmacologic treatment among comorbidity clusters were explored. Some of the results of this study have been previously reported in the form of an abstract (20).

METHODS

Please see the online supplement for details and references.

Study Design and Patients

The current analysis was based on data collected as part of the CIRO CO-morbidity (CIROCO) study, an observational single-center study. All subjects provided written informed consent and the study was approved by the local ethics and review boards (MEC 10-3-067). Patients with moderate to very severe COPD (Global Initiative for Chronic Obstructive Lung Disease [GOLD] grades II–IV [2]), aged 40–80 years, and in a clinically stable state were prospectively recruited between November 2007 and November 2010 during the initial evaluation of a comprehensive pulmonary rehabilitation program at CIRO (21). Patients with a history of asthma, α1-antitrypsin deficiency, any previous lung surgery, active inflammatory disease, acute myocardial infarction within the last 6 months, any known bone disease other than osteoporosis, current or recently (i.e., <5 yr before the study) treated malignant disease, or use of high-dose systemic glucocorticosteroids (i.e., >10 mg prednisolone) were excluded from the study.

Assessments

At study entry, patients’ demographics, smoking status, medications, and long-term oxygen use were documented. In addition, the following assessments were performed: lung function (post-bronchodilator spirometry, static lung volumes, and carbon monoxide transfer factor); body composition (BMI, fat free mass index, and bone mineral density at the hip, lumbar spine, and whole-body using dual-energy absorptiometry scan); vascular status (carotid intima-media thickness [c-IMT], diabetes [fasting glucose level >7.8 mmol/L or high-density lipoprotein cholesterol level <1.03 mmol/L in men or <1.29 mmol/L in women]; osteoporosis (T score less than −2.5); symptoms of anxiety and depression (HADS score ≥10 points); atherosclerosis (c-IMT >0.9 mm); and myocardial infarction (CIIS ≥20).

Definitions of Comorbidities

Thirteen comorbidities were identified in all patients based on predefined cut-offs as suggested by relevant international societies (see online supplement): chronic kidney disease (estimated glomerular filtration rate <60 ml/min); anemia (hemoglobin level <8.1 mmol/L in men and <7.5 mmol/L in women); hypertension (systolic blood pressure >140 mm Hg or diastolic pressure >90 mm Hg); obesity (BMI >30 kg/m²); underweight (BMI <21 kg/m²); muscle wasting (fat free mass index <16 kg/m² for men or <15 kg/m² for women); hyperglycemia (fasting glucose level >5.6 mmol/L); dyslipidemia (triglyceride level >1.7 mmol/L or high-density lipoprotein cholesterol level <1.03 mmol/L in men or <1.29 mmol/L in women); osteoporosis (T score less than −2.5); symptoms of anxiety and depression (HADS score ≥10 points); atherosclerosis (c-IMT >0.9 mm); and myocardial infarction (CIIS ≥20).

Statistics

All statistical analyses were performed using Viscovery Profiler 5.3 by Viscovery Software GmbH (www.viscovery.net; Vienna, Austria). Self-organizing maps (SOMs, also referred to as Kohonen maps) were used to create an ordered representation of the comorbidity data. The SOM method can be viewed as a nonparametric regression technique that converts multidimensional data spaces into lower dimensional abstractions. A SOM generates a nonlinear representation of the data distribution and allows the user to identify homogenous data groups visually.

Patients have been ordered by their overall similarity concerning their present comorbidities and also by the degree of its presence given by parameters from which the comorbidities are calculated. Based on the created SOM model, clusters have been generated using the SOM-Ward Cluster algorithm of Viscovery, a hybrid algorithm that applies the classical hierarchical method of Ward on top of the SOM topology. Summary variables on comorbidities and clinical characteristics for the study sample and for each cluster are presented as mean ± standard deviation for quantitative variables, and percentage for discrete variables. Data of the inflammatory markers were log-transformed to mitigate the effects of extreme values. Here, summary variables are presented as geometric mean with lower and upper limit. Viscovery automatically identified for each cluster the comorbidities, clinical characteristics, and inflammatory markers that differ significantly from the average of the whole study sample of 213 patients using the integrated two-sided t test with a confidence of 95%.

RESULTS

General Patient Characteristics

Of 255 patients prospectively recruited from patients admitted to CIRO, 42 were ineligible. The final study population consisted of 213 patients with moderate to severe COPD, substantial smoking history, moderately impaired diffusion capacity, and increased static lung volumes (Table 1). In 30 patients, data on one of the selected comorbidities was missing: 13 patients lacked acceptable quality c-IMT measurement, 6 did not fill out the HADS, and 11 lacked an acceptable ECG, impeding to determine the CIIS. Data on the self-reported (age-adjusted) Charlson comorbidity index are in the online supplement (see E1).

Frequency of Objectively Identified Comorbidities

All comorbidities were present in the COPD population, although the frequencies ranged from 5–54% (Figure 1). Hyperglycemia, atherosclerosis, hypertension, dyslipidemia, and osteoporosis were the five most prevalent comorbidities.

Number of Comorbidities

Almost all subjects (97.7%) had one or more comorbidities and more than half of the patients had at least four comorbidities (Figure 2). The frequencies of different individual comorbidities in patients with each of the 13 specific comorbidities are shown in Figure 3. For example, muscle wasting and osteoporosis were highly prevalent in underweight patients, whereas they were almost absent in obesity.
Comorbidity Clusters

Five clusters with a significantly different comorbidity profile were identified (Figure 4, Table 2). Cluster 1 (less comorbidity cluster) had significantly fewer comorbidities compared with the other clusters. Cluster 2 (cardiovascular cluster) had a significantly higher prevalence of hypertension and atherosclerosis compared with the other clusters. However, dyslipidemia, hyperglycemia, underweight, and muscle wasting were less prevalent compared with the other clusters. Cluster 3 (cachectic cluster) had a higher prevalence of underweight, muscle wasting, osteoporosis, and renal impairment, whereas obesity and atherosclerosis were less often identified. This cluster had a high number of comorbidities. Cluster 4 (metabolic cluster) also had a higher number of comorbidities. This cluster contained more patients with obesity, atherosclerosis, dyslipidemia, hyperglycemia, and hypertension, but fewer patients with anxiety, underweight, muscle wasting, and osteoporosis. Finally, cluster 5 (psychological cluster) had the highest proportion of patients with psychological disorders (anxiety and depression), but also the highest prevalence of myocardial infarction. A detailed description of the five clusters is presented in Table 2.

**Differences in Patient Characteristics among Clusters of Comorbidity**

FEV$_1$ (% predicted), smoking history, functional exercise capacity, long-term oxygen use, and updated BODE scores were not different among the comorbidity clusters (Table 3).

However, patients in cluster 1 (less comorbidity cluster) had a lower mean age, a higher mean diffusion capacity, and a better mean health-related quality of life. Moreover, a higher proportion of patients used cholesterol-lowering drugs, antiaggregates, or oral antidiabetics (see Table E2). Cluster 2 (cardiovascular cluster) included older patients who were less frequently active smokers but with a worse quality of life and a higher predicted cardiovascular risk according to the Framingham risk score. Cluster 3 (cachectic cluster) had a higher proportion of women and active smokers. In addition, patients in this cluster had on average more static hyperinflation and lower diffusion capacity. Surprisingly, they also had on average a lower dyspnea score, a better health-related quality of life, and a lower cardiovascular risk prediction score. In line with this, a lower proportion of patients in this cluster used cholesterol-lowering drugs or antihypertensive therapy, in particular, angiotensin-converters, angiotensin receptor blockers. Patients in cluster 4 (metabolic cluster) were more frequently male, had less static hyperinflation, and had on average a higher cardiovascular risk prediction score. Also, the proportion of patients using long-acting β-agonists and inhaled corticosteroid inhalers or short-acting rescue medication was lower in this cluster (see Table E3). Patients in cluster 5 (psychological cluster) reported on average more dyspnea and a worse health-related quality of life. Patients in this cluster more frequently used benzodiazepines and nitrates, as also short-acting “rescue” bronchodilators.

**Systemic Inflammation**

Table 4 shows circulating levels of inflammatory markers in the five identified clusters. Figure E1 shows the data point distribution of all inflammatory markers for each cluster. There were no significant differences in CRP, IL-8, or leukocytes among comorbidity clusters. TNF-R1 and TNF-R2 were significantly increased in the metabolic cluster compared with the whole COPD population. TNF-R1 was lower in the cachectic cluster and IL-6 was increased in the cardiovascular cluster.

**DISCUSSION**

In a cohort of moderate to very severe patients with COPD, five clusters of clinically important and objectively diagnosed comorbidities were identified. Although disease severity was comparable among comorbidity clusters, they were markedly different in terms...
of health status. Mostly, inflammatory markers were comparable among the clusters, although increased levels of TNF receptors were observed in the metabolic cluster and increased levels of IL-6 in the cardiovascular cluster.

Multiple studies have shown that comorbid chronic conditions occur more frequently in patients with COPD than in subjects without COPD and contribute to adverse clinical outcomes in these patients (1, 4–13). Moreover, the frequency of comorbidities was shown to be independent of the degree of airflow limitation (1, 8). In the present study, comorbidity clusters also had similar degree of airflow limitation.

Previous studies used self-reported comorbidities (1, 4–13) or healthcare databases that were not specifically designed to evaluate comorbidities (4, 9, 10, 13). These methods most probably underestimate the true prevalence of comorbidities in COPD. Here, 13 clinically relevant and well-known comorbidities were diagnosed using predefined internationally accepted cut-offs in a moderately sized, well-characterized sample of patients with COPD.
COPD. This study confirms the high frequency of individual comorbidities reported previously.

In the general population, there is a growing public attention to the concept of multimorbidity, because the presence of multiple chronic morbidities is associated with poor outcome and increased health care use (22). Only a few studies have investigated the coexistence of two or more comorbidities in individuals with COPD. For example, Siebeling and colleagues (11) reported an overlap in (self-reported) diabetes, musculoskeletal conditions, and cardiovascular disease in primary care patients with COPD. The present study is the first to identify clusters of objectively identified comorbidities in patients with COPD. The unbiased

![Figure 4. Multimorbidity clusters in chronic obstructive pulmonary disease (COPD). These panels were generated using Viscovery (Vienna, Austria) software. The Viscovery program placed all subjects on a specific position on the map based on their profile of comorbidities. The more subjects resemble in terms of their comorbidity the closer they are on the map. Contrarily, the more they differ the further they are away from each other. When looking at a comorbidity, subjects “raise a red flag” if the comorbidity is present and “a blue flag” when absent. In this way the maps can be interpreted. By drawing lines on the map, the Viscovery program could identify five different clusters of patients with COPD with a significant different profile of comorbidities (95% confidence interval).](image)

| TABLE 2. DETAILED DESCRIPTION OF THE FIVE CLUSTERS IN TERMS OF THE NUMBER OF COMORBIDITIES AND THE PREVALENCE OF EACH COMORBIDITY |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Comorbidities   | Cluster 1: Less Comorbidity | Cluster 2: Cardiovascular | Cluster 3: Cachectic | Cluster 4: Metabolic | Cluster 5: Psychologic |
| N               | 67              | 49              | 44              | 33              | 20              |
| Number of comorbidities | 2.5 ± 1.4* | 3.8 ± 1.7 | 4.2 ± 1.4† | 4.4 ± 1.1† | 4.1 ± 1.8 |
| Renal impairment, % | 16              | 24              | 45†            | 9               | 5               |
| Anemia, %       | 9               | 4               | 2              | 3               | 5               |
| Hypertension, % | 3*              | 98†             | 43             | 100†            | 5*              |
| Obesity, %      | 30              | 14              | 0†             | 61†             | 15              |
| Underweight, %  | 0*              | 0†              | 66†            | 3*              | 0               |
| Muscle wasting, %| 12*             | 10*             | 98†            | 0*              | 20              |
| Hyperglycemia, %| 52              | 41†             | 43             | 91†             | 60              |
| Dyslipidemia, % | 42              | 16*             | 25             | 67†             | 40              |
| Osteoporosis, % | 27              | 37              | 52†            | 0*              | 35              |
| Anxiety, %      | 5*              | 28              | 26             | 0*              | 84†             |
| Depression, %   | 6*              | 23              | 7              | 6               | 68†             |
| Atherosclerosis, %| 56             | 67†             | 12*            | 81†             | 53              |
| Myocardial infarction, % | 2*              | 11              | 7              | 13              | 32†             |

Summary variables are presented as mean ± standard deviation for quantitative variables, and percentage for discrete variables.

* Less prevalent compared with the whole study sample (95% confidence interval).
† More prevalent compared with the whole study sample (95% confidence interval).
TABLE 3. CLINICAL CHARACTERISTICS OF THE SUBJECTS IN THE FIVE CLUSTERS

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Cluster 1: Less Comorbidity</th>
<th>Cluster 2: Cardiovascular</th>
<th>Cluster 3: Cachectic</th>
<th>Cluster 4: Metabolic</th>
<th>Cluster 5: Psychologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>67</td>
<td>49</td>
<td>44</td>
<td>33</td>
<td>20</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>62.1 ± 6.8*</td>
<td>67.2 ± 5.8†</td>
<td>62.5 ± 7.2</td>
<td>63.1 ± 7.3</td>
<td>62.8 ± 6.8</td>
</tr>
<tr>
<td>Male, %</td>
<td>60</td>
<td>65</td>
<td>65</td>
<td>65†</td>
<td>45</td>
</tr>
<tr>
<td>mMRC dyspnea grade</td>
<td>1.99 ± 1.01</td>
<td>2.29 ± 1.21</td>
<td>1.73 ± 0.9*</td>
<td>2.12 ± 1.11</td>
<td>2.84 ± 1.12†</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>30</td>
<td>16†</td>
<td>16*</td>
<td>16*</td>
<td>35</td>
</tr>
<tr>
<td>Pack-years</td>
<td>44 ± 20</td>
<td>45 ± 26</td>
<td>49 ± 30</td>
<td>51 ± 34</td>
<td>42 ± 16</td>
</tr>
<tr>
<td>LTOT, %</td>
<td>13</td>
<td>18</td>
<td>18</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>6MWD, m</td>
<td>474 ± 102</td>
<td>446 ± 133</td>
<td>496 ± 101</td>
<td>473 ± 91</td>
<td>459 ± 74</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>52.7 ± 17.4</td>
<td>50.9 ± 17.7</td>
<td>48.3 ± 16.3</td>
<td>54.2 ± 16</td>
<td>48.3 ± 15.4</td>
</tr>
<tr>
<td>ITGV, % predicted</td>
<td>143 ± 33</td>
<td>148 ± 29</td>
<td>166 ± 34†</td>
<td>134 ± 33*</td>
<td>146 ± 28</td>
</tr>
<tr>
<td>TCLO, % predicted</td>
<td>60 ± 16†</td>
<td>57 ± 18</td>
<td>44 ± 13*</td>
<td>60 ± 14</td>
<td>55 ± 14</td>
</tr>
<tr>
<td>SGRQ total score</td>
<td>47.6 ± 15.3†</td>
<td>56.5 ± 17.2†</td>
<td>45.8 ± 19.4*</td>
<td>49.9 ± 16.1</td>
<td>65.9 ± 12.5†</td>
</tr>
<tr>
<td>SGRQ symptoms, score</td>
<td>49.1 ± 18.1†</td>
<td>58.8 ± 20.7</td>
<td>55.5 ± 23.1</td>
<td>52.8 ± 20.2</td>
<td>69.9 ± 14.4‡</td>
</tr>
<tr>
<td>SGRQ activity, score</td>
<td>68.3 ± 20.2</td>
<td>70.2 ± 22.0</td>
<td>60.4 ± 24.9*</td>
<td>66.4 ± 20.9</td>
<td>83.5 ± 13.9†</td>
</tr>
<tr>
<td>SGRQ impact, score</td>
<td>36.3 ± 17.9</td>
<td>43.6 ± 21.2</td>
<td>35.1 ± 21.5</td>
<td>39.6 ± 18.1</td>
<td>52.6 ± 16.6‡</td>
</tr>
<tr>
<td>Updated BODE score</td>
<td>2.4 ± 2.6</td>
<td>3.4 ± 3.3</td>
<td>3.0 ± 1.8</td>
<td>2.6 ± 2.3</td>
<td>3.1 ± 1.9</td>
</tr>
<tr>
<td>Framingham 10-yr risk, %</td>
<td>8.6 ± 6.6</td>
<td>11.5 ± 6.6†</td>
<td>7.6 ± 6*</td>
<td>11.9 ± 7.3†</td>
<td>6.6 ± 4.5</td>
</tr>
</tbody>
</table>

Definition of abbreviations: 6MWD = 6-minute walking distance; BODE = body mass index, obstruction (FEV1), dyspnea, exercise (6MWD); ITGV = intrathoracic gas volume; LTOT = long-term oxygen therapy; mMRC = Modified Medical Research Council; TLCO = transfer factor for carbon monoxide; SGRQ = St. George’s Respiratory Questionnaire.

Summary variables are presented as mean ± standard deviation for quantitative variables, and percentage for discrete variables.

* Less prevalent compared with the whole study sample (95% confidence interval).
† More prevalent compared with the whole study sample (95% confidence interval).

approach to identify these comorbidity clusters is a major strength of the current analyses. Indeed, the use of self-organizing maps may be the most compact way to represent a data distribution, because data dependency can be understood easily if one is familiar with the map visualization.

Cluster analyses have been used before in patients with COPD (23–26). Only two studies (24, 25) used comorbidities in their cluster analyses, which also included all types of other clinical characteristics. Both studies identified a comorbidity–predominant subtype of patients with milder respiratory status but a higher prevalence of obesity, cardiovascular disease, and diabetes. In the PAC-COPD cohort, also higher levels of systemic inflammatory markers were identified in that cluster (24). These clusters seem to resemble the metabolic cluster in the present study.

In total, five distinct clusters were recognized based on the comorbidity profiles. Patients in the cachectic cluster had a lower diffusion capacity and more static hyperinflation compared with the other clusters, which probably is consistent with a higher amount of emphysema. Previously, osteoporosis and renal impairment (27, 28) were associated with emphysema, and osteoporosis was linked to muscle wasting (29). This suggests that there may be a common pathophysiologic pathway for the cooccurrence of these chronic conditions.

Contrary to the cachectic cluster, a metabolic cluster was identified. These patients had less severe pulmonary impairment compared with the other clusters, but more pronounced metabolic disorders and a low-grade systemic inflammation. The identification of these two distinct clusters is reminiscent of the historical description of the pink puffer (emphysematous type with a cachectic impression) and the blue bloater (chronic bronchitis type with a metabolic impression) (30).

Despite comparable increased cardiovascular risk according to the Framingham risk score, the cardiovascular cluster, characterized by increased blood pressure and “subclinical” atherosclerosis, was clearly different from the metabolic cluster. The former cluster had significantly less obesity, dyslipidemia, or hyperglycemia, and a different inflammatory marker is increased (IL-6 in the cardiovascular cluster, compared with TNF receptors in the metabolic cluster). This suggests that different pathways may be involved in the development of cardiovascular comorbidity in COPD.

A large subgroup of patients with significantly less comorbidity was clustered. These patients were younger and a higher proportion was treated with oral antidiabetics and cholesterol-lowering drugs. This may partially explain why these patients had less comorbidity.

The psychologic cluster, including a high proportion of patients with increased symptoms of anxiety and depression, and ischemic heart injury, is considered an important finding. Indeed, anxiety was reported to be the strongest independent predictor of mortality in patients with COPD (5). The (unbiased) recognition of a psychopathologic cluster is consistent with growing literature as mental conditions are recognized as a relevant factor of multimorbidity in the general population (31). The high prevalence of

TABLE 4. INFLAMMATORY MARKERS AMONG THE FIVE CLUSTERS

<table>
<thead>
<tr>
<th></th>
<th>Cluster 1: Less Comorbidity</th>
<th>Cluster 2: Cardiovascular</th>
<th>Cluster 3: Cachectic</th>
<th>Cluster 4: Metabolic</th>
<th>Cluster 5: Psychologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP, ng/ml</td>
<td>2,286 (844, 6,188)</td>
<td>3,380 (947, 12,062)</td>
<td>2,005 (677, 5,938)</td>
<td>3,860 (1,073, 13,886)</td>
<td>2,519 (767, 8,283)</td>
</tr>
<tr>
<td>IL-6, pg/ml</td>
<td>2.4 (1.3, 4.3)</td>
<td>3.4 (1.8, 6.6)*</td>
<td>2.2 (1.1, 4.7)</td>
<td>2.7 (1.6, 4.5)</td>
<td>2.2 (1.3, 3.6)</td>
</tr>
<tr>
<td>IL-8, pg/ml</td>
<td>12.3 (8.2, 18.6)</td>
<td>12.9 (9.3, 17.9)</td>
<td>12.1 (7.8, 18.7)</td>
<td>10.8 (7.6, 15.2)</td>
<td>11.1 (6.6, 18.7)</td>
</tr>
<tr>
<td>TNF-R1, pg/ml</td>
<td>2,013 (1,508, 2,689)</td>
<td>2,229 (1,513, 3,285)</td>
<td>1,896 (1,434, 2,505)†</td>
<td>2,377 (1,850, 3,055)*</td>
<td>2,133 (1,685, 2,699)</td>
</tr>
<tr>
<td>TNF-R2, pg/ml</td>
<td>3,417 (2,454, 4,758)</td>
<td>3,698 (2,399, 5,701)</td>
<td>3,302 (2,478, 4,401)</td>
<td>4,080 (3,115, 5,344)*</td>
<td>3,419 (2,675, 4,371)</td>
</tr>
<tr>
<td>Leukocytes, ×10³/L</td>
<td>7.3 (5.6, 9.5)</td>
<td>7.1 (5.5, 9.4)</td>
<td>7.0 (5.3, 9.1)</td>
<td>7.2 (5.9, 8.7)</td>
<td>7.3 (6.0, 8.9)</td>
</tr>
</tbody>
</table>

Definition of abbreviations: CRP = C-reactive protein; TNF = tumor necrosis factor.

Data were log-transformed to mitigate the effects of extreme values. Summary variables are presented as geometric mean (lower and upper limit).

* More prevalent compared with the whole study sample (95% confidence interval).
† Less prevalent compared with the whole study sample (95% confidence interval).
anxiety and depression after myocardial infarction may explain the high proportion of patients with ECG abnormalities in this cluster (32). Whether and to what extent the higher prevalence of ECG abnormalities in anxious patients with COPD may explain the worse prognosis in these patients remains unknown.

A direct link between (chronic low-grade) systemic inflammation and comorbidities in patients with COPD remains equivocal. For example, bivariate associations among various systemic inflammatory biomarkers and pulmonary cachexia (33), subclinical atherosclerosis (34), metabolic syndrome (35), and ischemic heart disease have been reported in patients with COPD (36). Moreover, CRP, fibrinogen, and leukocyte count were associated with increased risk of comorbidities in patients with COPD (18). Then again, many studies showed comparable circulating levels of inflammatory biomarkers in patients with COPD with and without comorbidities, such as cachexia (37), osteoporosis (38), cardiovascular disease (39), and depression (40). So, a causal relationship between low-grade systemic inflammation and comorbidities in COPD has not yet been proved. The current findings also show that the possible interactions between biomarkers of systemic inflammation and comorbidities in patients with COPD are very complex, if present at all.

Chronic low-grade systemic inflammation is a hallmark of obesity in the general population (41), suggesting a systemic origin of inflammation. Increased levels of systemic inflammation have also been reported in patients with COPD, in particular in patients who are obese (19, 42–44). This may partially explain the low-grade systemic inflammation in the metabolic cluster, and its lesser presence in the cachectic cluster. Similarly, the increased IL-6 in the cardiovascular cluster might be caused by the significant older age in that cluster. Indeed, a wealth of data indicates that normal aging is associated with low-grade systemic inflammation, including IL-6 (45).

Methodologic Considerations

The present study included GOLD grade II–IV patients. Therefore, the current finding should not be extrapolated to GOLD grade I patient subsets. Moreover, patients were recruited in a tertiary care pulmonary rehabilitation setting, which may also limit the external validity of the current findings. However, the following arguments do support the generalizability of our findings to a broader population. The prevalence of objectively identified renal impairment in our study was similar to results in patients with COPD attending the pulmonary medicine outpatient facilities of 15 centers located throughout Italy (46). Furthermore, the Charlson comorbidity index score in the present study (1.6 ± 0.9 points; age-adjusted, 3.5 ± 1.3 points) was comparable with the PAC-COPD cohort (2 ± 1.3 points) (24), and the ESMI cohort (3.1 ± 2 points), respectively (47). Furthermore, the prevalence of self-reported cardiovascular comorbidities (as recorded in the Charlson comorbidity index) in the present study was comparable with previous studies (1, 5, 19). Thus, the prevalence of comorbidities in the present study seems comparable with data obtained in the secondary outpatient care setting.

Another limitation considering comorbidities might be that patients with active malignant diseases, active inflammatory diseases, or recent myocardial infarction were excluded from participation in the study because these patients are not suitable for pulmonary rehabilitation.

Although the elected biomarkers in the present study are well studied in COPD, it should be mentioned that the concept of systemic inflammation is more complex than that which can be captured in a short series of biomarkers. The strength of measuring comorbidities in an objective manner brings with it the limitation of having evaluated only a limited number of comorbidities. Because of logistical constraints, chronic heart failure, obstructive sleep apnea, and degenerative joint disease were not assessed, although it is known that these conditions are common in COPD (5). Also, it is desirable to validate the current findings in an external replication cohort. In addition, it would be interesting to evaluate clusters of comorbidities in subjects with another index disease (e.g., diabetes mellitus) and in the general population. Furthermore, the longitudinal stability of comorbidity clusters and the prognostic outcome of the different clusters are interesting future research questions.

This is the first study that objectively identified multiple comorbidities in a well-characterized cohort of patients with COPD. The self-organizing maps are new in the field of COPD research and provide easy-to-use graphs of the five independent comorbidity clusters that were identified. The current findings will increase the awareness among physicians that multiple comorbidities can be present in patients with COPD. This will also enhance treatment strategies and facilitate the combination of future treatment guidelines for different comorbidities. Interestingly, the degree of airflow limitation, exercise capacity, and score on the updated BODE index were similar among the comorbidity clusters. This emphasizes the fact that comorbidities are an additional clinical attribute in patients with COPD, which cannot be predicted by the aforementioned clinical outcomes. In addition, low-grade systemic inflammation was mostly comparable among comorbidity clusters. This shows that the presumed association between systemic inflammation and comorbidities in patients with COPD is more complex than assumed at present.

Author disclosures are available with the text of this article at www.atsjournals.org.

References