Validation of Clinical COPD Phenotypes for Prognosis of Long-Term Mortality in Swedish and Dutch Cohorts


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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease with variable mortality risk. The aim of our investigation was to validate a simple clinical algorithm for long-term mortality previously proposed by Burgel et al. in 2017. Subjects with COPD from two cohorts, the Swedish PRAXIS study (n=784, mean age (SD) 64.0years (7.5), 42% males) and the Rotterdam Study (n=735, mean age (SD) 72years (9.2), 57% males), were included. Five clinical clusters were derived from baseline data on age, body mass index, dyspnoea grade, pulmonary function and comorbidity (cardiovasculace disease/diabetes). Cox models were used to study associations with 9-year mortality. The distribution of clinical clusters (1–5) was 29%/45%/8%/6%/12% in the PRAXIS study and 23%/26%/36%/9%/15% in the Rotterdam Study. The cumulative proportion of deaths at the 9-year follow-up was highest in clusters 1 (65%) and 4 (72%), and lowest in cluster 5 (10%). Burgel's age- and sex-adjusted hazard ratio (95% confidence interval) for cluster 1 was 6.37 (3.94–10.32) and those for clusters 2 and 3 were 2.61 (1.58–4.32) and 3.06 (1.82–5.13), respectively. Burgel's clinical clusters can be used to predict long-term mortality risk. Clusters 1 and 4 are associated with the poorest prognosis, cluster 5 with the best prognosis and clusters 2 and 3 with intermediate prognosis in two independent cohorts from Sweden and the Netherlands.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death and associated with high healthcare and societal costs worldwide [1]. The estimated prevalence of COPD in different populations varies widely depending on the criteria used. For example, a prevalence of around 9–10% could be found based on objective measurements, while the prevalence of doctor’s diagnosed COPD was around 5%, indicating the disease is still under-recognised [2]. According to the Global Initiative for Obstructive Lung Disease (GOLD), a post-bronchodilator fixed ratio of forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) lower than 0.70 is required to establish the diagnosis in subjects with respiratory symptoms and relevant exposure, and therefore clinical suspicion of COPD [3].

The clinical grading used for prognosis of COPD encompasses airflow obstruction severity (FEV1), degree of respiratory symptoms and history of exacerbations [4], including hospitalisations. However, other factors than these – for example comorbidities such as heart failure (HF), coronary cardiovascular disease (CVD), diabetes, depression and lung cancer, as well as lung function decline[5] – have a major impact on prognosis.

COPD is a highly heterogeneous disease with large differences in exacerbation rate or mortality between patients. It is therefore important to find new predictive factors that would guide classification of patients to different risk groups.

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Many studies have tried to explore the disease heterogeneity; one of the first attempts involved dividing subjects into two groups – ‘pink puffers’ and ‘blue bloaters’ – based on physical findings [6]. Several previous studies have applied cluster analysis [7] to derive distinct patient subgroups and find their associations with clinically relevant outcomes such as cohort mortality [8–10] or predicted mortality scores [11, 12], hospital admissions [10] and frequency of exacerbations [13, 14]. Nevertheless, the majority of studies have lacked external validation and the results of cluster analysis have given no tool for individual patient allocation to the described phenotypes. A systematic review could identify two consistent major clinical phenotypes with poor prognosis across multiple studies: younger patients with severe COPD and low probability of cardiovascular comorbidities and older individuals with moderate respiratory disease and high prevalence of comorbidities, obesity and inflammatory markers [15].

Burgel et al. [16] recently investigated COPD cohorts using cluster analysis and identified five subgroups with different rates of 3-year all-cause mortality. Further classification and regression trees (CART) [17] were used to develop an algorithm to allocate patients to those subgroups. The data needed for these clinical clusters can be collected at regular patient follow-ups and integrate respiratory variables and comorbidities (cardiovascular diseases, diabetes and obesity). Although the authors validated their findings in an independent COPD cohort with regard to 3-year mortality, no validation has been performed beyond the 3-year timeframe investigated in the original publication.

Our aim was therefore to evaluate the prognostic value of this clinical clustering algorithm over an extended follow-up time, 9–12 years, in two prospective cohorts in Sweden and the Netherlands.

**Methods**

**Study design**

Patient data from Swedish and Dutch COPD cohorts, presented in the next section, were used to allocate subjects into specific phenotype groups in accordance with the algorithm published by Burgel et al. [16], based on age, body mass index (BMI), lung function, comorbidities and dyspnoea (Figure 1).

**COPD cohorts and COPD diagnosis**

The Rotterdam Study is a prospective population-based cohort study ongoing since 1990 in Ommoord, a suburb of the city of Rotterdam, Netherlands. The objective of the study is to clarify the risk factors (genetic, environmental and lifestyle) of diseases in an ageing population. Diseases targeted are cardiovascular, respiratory, endocrine, hepatic, neurological, ophthalmic, psychiatric, dermatological, otolaryngological and locomotor [18]. The study consists of four cohorts with a total of more than 15,000 subjects aged ≥ 45 years. Every 3–4 years, participants undergo a home interview and clinical examinations at the research centre. For the purpose of this study, we analysed participants from the fifth round of the Rotterdam Study, visiting the research centre during 2009–2014. A total of 5,487 participants had performed spirometry, of whom 5459 also consented to a follow-up. FEV$_1$/FVC ratio < 0.7, for example, airflow obstruction, was found in 912 subjects. COPD was defined as presence of airflow obstruction in absence of a clinical asthma diagnosis, leaving 806 individuals in the present study. Among them, 71 individuals could not be classified in accordance with the Burgel algorithm, due to missing

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**Figure 1.** Allocation algorithm based on Burgel et al. for the PRAXIS (PS) and Rotterdam Study (RS) cohorts.
data from the modified Medical Research Council (mMRC) dyspnoea scale score (Online Figure S1).

The PRAXIS study is a prospective COPD cohort created in 2005. It includes primary and secondary care patients, randomly selected, from 56 primary health care centres and 14 hospitals in central Sweden, that answered a detailed questionnaire [19]. COPD diagnosis was based on medical records, for example, physician-diagnosed COPD in the medical records. A total of 1,088 individuals fulfilled the inclusion criteria for our study. However, 304 of them could not be classified in the Burge1 clusters due to missing data, leaving 784 individuals in the present analyses (Online Figure S1).

**Short-term oral corticosteroid use**

Information on short-term oral corticosteroid use in the 6 months prior to entering the study was available for both cohort and used as a marker for recent exacerbations. In the PRAXIS study, this data was taken from questionnaires. In the Rotterdam Study, complete information on all filled prescriptions for steroids and/or antibiotics on a day-to-day basis was obtained from pharmacies and validated.

**Exacerbations**

Information about exacerbations during the 6 months prior to inclusion in the study was retrieved from the questionnaire in the PRAXIS study. Exacerbations were defined as emergency visits to primary care or secondary care (outpatient or hospitalisation) due to deterioration of their lung disease, or need for an oral steroid course, in the 6 months preceding inclusion.

**Dyspnoea**

Dyspnoea grade was measured on the mMRC dyspnoea scale and obtained through questionnaires. This scale has been validated before and is often used in research and clinical settings [20].

**Comorbidities**

Information about cardiovascular comorbidities (hypertension, ischaemic heart disease and chronic heart failure), asthma and diabetes was taken from patients’ records in the PRAXIS study [21]. In the Rotterdam Study, relevant data for each patient were obtained at baseline and at follow-up, via a combination of objective measures, reviews of medical record reviews from primary and secondary care and prescription registries. For example, hypertension in the Rotterdam Study was defined as a systolic blood pressure (SBP) > 140 mmHg, diastolic blood pressure (DBP) > 90 mmHg, or use of blood pressure-lowering medication for the indication hypertension. SBP and DBP were measured in the right upper arm with the subjects in a seated position. The average of two consecutive measurements was taken. Definitions of cardiovascular comorbidities in the Rotterdam Study are described in detail elsewhere [22].

**Smoking habits**

Current smoking status was also questionnaire-assessed and the patients were divided into current and non-smokers for the purpose of this study.

**Lung function tests**

FEV₁ was expressed as % predicted pre-bronchodilator spirometry in the Rotterdam Study, using Global Lung Initiative reference equations [23]. Lung function tests were performed by trained paramedical personnel in accordance with the American Thoracic Society/European Respiratory Society Task Force 2005 document regarding standardisation of spirometry [24]. A portable spirometer (SpiroPro; Erich Jaeger GmbH; Hoechberg, Germany) was used from 2002 to 2008 and a Master Screen® PFT Pro (Care Fusion, the Netherlands) was used from 2009 onward [25, 26].

FEV₁ was recorded in the PRAXIS study as the highest % predicted of any pre- or post-bronchodilator values from spirometry reports or medical records, using European Community for Steel and Coal reference values [27], from the review of medical records between 2000 and 2004. These values has been registered only as percent predicted and no exact date of the spirometry was recorded in the database. As the data were collected from clinical practice, several different spirometry devices, such as pneumotachographs, ultrasound sensors or turbine transducers, from several manufacturers were used [28].

**Statistical analysis**

Descriptive statistics were used for analysing the prevalence of each cluster and characteristics of individuals within each cluster. Survival analyses for all-cause mortality were performed at 3 and 9 years for both cohorts and also at 12 years for the PRAXIS study. We used both Kaplan-Meier curves and Cox models. Meta-analyses of the Cox models for 3- and 9-year survival were also performed. Adjustments were made for age, sex or both age, sex and short-term oral corticosteroid use. STATA software version 16 (StataCorp LLC, College Station, TX, USA) and R version 4.3.0.2 were used for the analyses.

**Ethics**

In both studies, all patients signed informed consent prior to participation. The Rotterdam Study was approved by the Ethical Committee of the Erasmus Medical Centre (Rotterdam, the Netherlands) and the review board of the Netherlands Ministry of Health, Welfare and Sports (1068889-159521-PG). The PRAXIS study was approved by the Regional Ethical Review Board in Uppsala, Sweden (Dnr 2004: M-445 and Dnr 2010/090).
**Results**

The characteristics of subjects with COPD in both cohorts at inclusion are presented in Table 1. In the Rotterdam study, subjects were slightly older, had better lung function (FEV₁ (% predicted)), less dyspnoea (mMRC), and less reported use of short-term oral corticosteroids during the preceding 6 months, but more cardiovascular comorbidities, especially hypertension (Table 1).

The algorithm for allocation of patients into five clinical clusters (1–5) in the PRAXIS and Rotterdam studies is presented in Figure 1 and the characteristics of the subjects included in the respective clusters are presented in Tables 2A and B. In the PRAXIS study, cluster 5 was characterised by the lowest mortality rate at all timepoints, while the highest 9-year mortality rates of 65% and 72% were observed in clusters 1 and 4, respectively. In the Rotterdam study, the patients could be classified into only four clinical clusters (1, 2, 3 and 5), as no subjects fulfilled the criteria for cluster 4 (no cardiovascular comorbidities, severe dyspnoea and FEV₁ ≤ 35% predicted) (Figure 1). The lowest mortality rate was found in cluster 5. Cluster 1 had the highest mortality rate at both 3 and 9 years; cluster 3 had intermediate mortality rates (Table 2B). Cluster 2 had mortality rates in between cluster 5 and cluster 3 (Table 2B). The findings reported above can be seen in the Kaplan-Meier plots, performed for each study separately with 9-year follow-up data in the Rotterdam Study and 12-year follow-up data in the PRAXIS study (Figures 2A and B).

Hazard ratios (HR) for mortality at 3, 9 and 12 years for the different clinical clusters were calculated using Cox regression, separately for each cohort (Table 3). In both cohorts, the worst prognosis during overall follow-up, based on the HR for mortality, was observed in clusters 1 and 4, and the best prognosis in cluster 5. Clusters 2 and 3 showed intermediate rates (Table 3).

Age- and sex-adjusted HR were also calculated (Table 4) and the results were consistent for most of the comparisons, with the exception of non-significant association of cluster 3 with 3-year survival in both studies. For the PRAXIS study, we performed an additional adjustment for asthma and the associations presented in Table 4 remained significant (Online Table 1). Lastly, further adjustment for short-term oral corticosteroid use during the six months prior to the study did not change the results presented in Table 4, with the exception of non-significant association of cluster 1 with 3-year survival and of cluster 3 with 9-year survival in the Rotterdam Study (Table 5). In the PRAXIS study, we also applied a model where adjustments for age and previous exacerbations were used, instead of adjustments for oral corticosteroids, with similar results (data not shown).

Meta-analyses of the age- and sex-adjusted Cox regression models for the two studies are presented in Table 6 and Online Table 2. Both clusters 1 and 3 had higher mortality risk than cluster 5 at 3 years, but cluster 2 did not (Table 6). Clusters 1, 2 and 3 had higher mortality risk at 9 years compared with cluster 5. Moreover, cluster 1 had worse prognosis than both clusters 2 and 3, with regard to both 3- and 9-year mortality (Online Table S2). Lastly, cluster 3 had worse prognosis than cluster 2, with regard to both 3- and 9-year mortality (Online Table S2).

A sensitivity analysis of using LLN instead of 0.70 as cut-off for abnormal FEV₁/FVC-ratio, and COPD diagnosis, was performed in the Rotterdam study. By using LLN instead of 0.70, only 286 subjects had confirmed COPD diagnosis and these were distributed as following: 90 in cluster 1, 96 in cluster 2, 66 in cluster 3 and 34 in cluster 5. Mortality rates at 3 and 9 years are presented in Supplementary Table 3 and these were similar to the ones presented in Table 2 of clusters 1, 2 and 3. No HR could be calculated in comparison with cluster 5 as all subjects in cluster 5 were alive at 9-years’ follow-up.

**Discussion**

We applied and validated the previous clinical clusters proposed by Burgel et al., based on comorbidities, lung
function, age, BMI and dyspnoea, and could confirm the predictive value of these clusters for long-term mortality, up to 9 and 12 years, in two different European COPD cohorts, respectively. We also found these results to be consistent after adjustments for age, sex, previous exacerbation rates and concurrent asthma. The worst prognosis, in both cohorts, was found for cluster 1, which comprised individuals with cardiovascular comorbidities and/or diabetes and high grade of dyspnoea and elderly individuals (> 70 years of age) with FEV$_1$ < 50% predicted. Cluster 4, comprising highly dyspnoeic individuals with FEV$_1$ ≤ 35% predicted, but without cardiovascular comorbidities or diabetes, was only present in the Swedish patient cohort, and also had a poor prognosis. On the other hand, cluster 5, including individuals without comorbidities, with a low grade of dyspnoea and preserved lung function (FEV$_1$ ≥ 60% predicted) was associated with the best prognosis in both cohorts.

Different score systems have been proposed to determine which COPD patients are at higher risk of mortality or worsening of disease. The BODE index, which encompasses four variables (BMI, grade of airflow obstruction, dyspnoea grade and exercise capacity) is a well-known score (on a scale of 0–10 points) to predict mortality [29]. The two extreme quartiles of the BODE index, quartile I (0–2 points) and quartile IV (7–10 points), may correlate with our study’s clusters 5 and 1, respectively. The quartiles were related to mortality of around 20% and 80%, respectively, at a 52-month follow-up [29]. Another known index,

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### Table 2A. Baseline characteristics of the clinical COPD phenotype groups in the PRAXIS cohort (mean (SD) or % unless otherwise stated).

<table>
<thead>
<tr>
<th>Cluster 5 (n=94)</th>
<th>Cluster 1 (n=229)</th>
<th>Cluster 2 (n=352)</th>
<th>Cluster 3 (n=66)</th>
<th>Cluster 4 (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.7 (9.0)</td>
<td>67.3 (6.2)</td>
<td>62.5 (7.1)</td>
<td>65.6 (6.5)</td>
</tr>
<tr>
<td>Female sex</td>
<td>68</td>
<td>53</td>
<td>61</td>
<td>47</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>25.6 (4.4)</td>
<td>27.1 (5.9)</td>
<td>25.1 (4.8)</td>
<td>30.7 (5.2)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>35</td>
<td>18</td>
<td>33</td>
<td>27</td>
</tr>
<tr>
<td>Asthma</td>
<td>32</td>
<td>38</td>
<td>36</td>
<td>32</td>
</tr>
<tr>
<td>FEV$_1$ % pred*</td>
<td>80.1 (16.4)</td>
<td>48.2 (19.1)</td>
<td>58.8 (20.6)</td>
<td>69.5 (19.1)</td>
</tr>
<tr>
<td>mMRC (median (IQR))</td>
<td>1 (0–4)</td>
<td>4 (3–6)</td>
<td>2 (1–2)</td>
<td>1 (1–2)</td>
</tr>
<tr>
<td>Any comorbidity</td>
<td>0</td>
<td>100</td>
<td>42</td>
<td>100</td>
</tr>
<tr>
<td>– Hypertension</td>
<td>0</td>
<td>53</td>
<td>27</td>
<td>74</td>
</tr>
<tr>
<td>– Diabetes</td>
<td>0</td>
<td>21</td>
<td>7</td>
<td>27</td>
</tr>
<tr>
<td>– IHD/CHF</td>
<td>0</td>
<td>62</td>
<td>18</td>
<td>45</td>
</tr>
</tbody>
</table>

### Table 2B. Baseline characteristics of the clinical COPD phenotype groups in the Rotterdam Study cohort (mean (SD) or % unless otherwise stated).

<table>
<thead>
<tr>
<th>Cluster 5 (n=109)</th>
<th>Cluster 1 (n=167)</th>
<th>Cluster 2 (n=195)</th>
<th>Cluster 3 (n=264)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.9 (8.2)</td>
<td>75.8 (7.5)</td>
<td>64.7 (6.3)</td>
</tr>
<tr>
<td>Female sex</td>
<td>50</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>24.9 (3.2)</td>
<td>27.6 (4.4)</td>
<td>25.5 (3.0)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>35 (32.1)</td>
<td>45 (26.9)</td>
<td>68 (34.9)</td>
</tr>
<tr>
<td>Asthma</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>FEV$_1$ % pred</td>
<td>88.3 (13.0)</td>
<td>63.2 (18.0)</td>
<td>78.6 (18.8)</td>
</tr>
<tr>
<td>mMRC</td>
<td>0.06 (0.25)</td>
<td>3.33 (1.07)</td>
<td>0.90 (1.24)</td>
</tr>
<tr>
<td>Any comorbidity</td>
<td>0</td>
<td>167 (100.0)</td>
<td>151 (77.4)</td>
</tr>
<tr>
<td>– Hypertension</td>
<td>0</td>
<td>160 (95.8)</td>
<td>143 (73.3)</td>
</tr>
<tr>
<td>– Diabetes</td>
<td>0</td>
<td>24 (14.5)</td>
<td>14 (7.2)</td>
</tr>
<tr>
<td>– IHD/CHF (combined)</td>
<td>0</td>
<td>77 (46.1)</td>
<td>20 (10.3)</td>
</tr>
</tbody>
</table>

---

Abbreviations: BMI, body mass index; CHF, chronic heart failure; FEV$_1$, forced expiratory volume in 1 s; IHD, ischaemic heart disease; mMRC, modified Medical Research Council dyspnoea scale.

Information available only in 549 subjects in PRAXIS study.
consisting of dyspnoea, obstruction, smoking and exacerbation (DOSE), showed increased risk of death: HR 8.00 for score 6–7 compared with HR 3.48 for score 0–3 in COPD patients from primary and secondary care within a period of five years [30]. Moreover, a meta-analysis on nearly 15,000 patients from 24 different cohorts concluded that the ADO (age, dyspnoea and airflow obstruction) index best predicted 3-year mortality in COPD patients, followed by the updated BODE index[31, 32]. Other scores are B-AE-D (BMI, acute exacerbations, dyspnoea) [33] and e-BODE (addition of exacerbations to BODE) [33]. A more recent study suggested that BODE
could be combined with information on comorbidities in order to increase its predictive value for mortality, creating the so-called COPD comorbidity test (COTE) index [34] – an approach close to the Burgeł’s algorithm [16]. Worse survival was noted in the presence of comorbidities for each BODE quartile when studying mortality for up to 54 months. Recently, we found indications that cardiovascular comorbidity, especially heart failure, myocardial infarction and stroke, predicted mortality in a Swedish real-world primary care study of COPD patients [35]. In line with this, a newer index has been proposed to be applied in the primary care setting and validated for short-term mortality – BARC (body mass index and blood results (B), age (A), respiratory variables, such as obstruction, exacerbations and smoking (R) and comorbidity (C)) [36]. A recent study suggested benefits from using comorbidities to improve the performance of ADO and DOSE in estimating mortality for up to 3 years in a primary care setting [37]. A recent meta-analysis on different prognostic instruments concluded that future research should focus on external validation of these prognostic instruments along with cost-effectiveness analyses [38].

Cluster 1 was consistently associated with poorer prognosis in both cohorts up to 9 or 12 years of follow-up. The cardiovascular and diabetes comorbidities have been shown to relate to poorer prognosis in several studies [39, 40]. Low values of FEV1, as well as higher grades of dyspnoea, are also associated with higher mortality and are already included in several prognostic score systems, that is, BODE or DOSE [29, 30, 41]..

Cluster 4 was present only in the Swedish cohort and was also associated with poor prognosis. The absence of cluster 4 in the Rotterdam study might be explained by the elderly population and a higher prevalence of hypertension (as blood pressure was measured during the clinical visit), which contributed to the majority of the participants with COPD in the Rotterdam Study having cardiovascular comorbidities as well. Moreover, the fact that these individuals were randomly selected from the population might have resulted in a very small proportion of subjects with severely impaired lung function (FEV1 ≤ 35% predicted).

Cluster 5, characterised by the absence of the comorbidities, low grade of dyspnoea (mMRC 0–1) and FEV1 ≥ 60%, had the best prognosis, with 90% survival at 9 year follow-up. In past studies, little attention has been paid to the clusters with good prognosis, although we are aware that some COPD patients have a very stable disease and do not have exacerbations [42].

A major strength of the present study was that we were able to validate the Burgeł clinical clusters in two different European cohorts: a Swedish patient cohort and a Dutch population-based cohort. There is a rationale for validating the instrument in several cohorts, as previous studies regarding the BODE index could demonstrate differing performance in different populations [43]. Another strength is the fact that we could validate the clusters for both short-term mortality (3 years) and long-term mortality (9–12 years). The mortality rates at 3-year follow-up were comparable between our two cohorts and with the replication cohort from Burgeł’s paper, where the majority of patients were recruited from population-based studies. Our study also had some limitations. For example, lung function in the PRAXIS study was not registered at study inclusion; the last recorded spirometry was retrieved from patient records. Moreover, different reference values for spirometry were used in our studies, depending on the respective national clinical practices. The COPD definition in the Rotterdam Study was mainly based on the pulmonary function testing results for a routine visit to research centre and did not require relevant exposure or respiratory symptoms, differing from the PRAXIS study, where only doctor-diagnosed patients with COPD were included. A limitation of the PRAXIS study is the fact that a large proportion of subjects were lacking the results of a post-bronchodilatory spirometry in the medical records reviewed between 2000 and 2004. This might be due to the fact that they had a diagnosis confirmed by spirometry before study entry or that patients with most severe disease have been unable or unwilling to perform a lung function test. Sundh et al. demonstrated in the present population that COPD subjects without lung function were actually characterised by a higher mortality than subjects with available lung function [30]. We interpret the poorer prognosis in these subjects without spirometry as an indirect confirmation that the subjects had COPD. Moreover as the results were consistent across the two studies, this suggests that the clusters are valid in different populations. Lastly, the present clusters do not include exacerbations in their definitions, although exacerbations are known to be strong predictors for future exacerbations and mortality [4]. However, we found that the prognostic value for clinical clusters was independent of previous use of short-term oral corticosteroid treatment, used as a proxy for previous exacerbations.

In conclusion, we could validate previously proposed clinical phenotypes with regard to long-term mortality in two different European cohorts. We could validate clusters associated with both good and bad prognosis. These clinical clusters are based on data that is easy available at the patient visit as it does not requiring extensive characterisation of patients or specific

<table>
<thead>
<tr>
<th>Cluster</th>
<th>3 years</th>
<th>9 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 (ref)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>6.32 (2.64–15.12)</td>
<td>6.37 (3.94–10.32)</td>
</tr>
<tr>
<td>2</td>
<td>1.55 (0.60–4.03)</td>
<td>2.61 (1.58–4.32)</td>
</tr>
<tr>
<td>3</td>
<td>3.40 (1.37–8.47)</td>
<td>3.06 (1.82–5.13)</td>
</tr>
<tr>
<td>4</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Table 6. Meta-analysis for relative mortality risk at 3 and 9 years, adjusted for age and sex. Cox regression model (HR, 95% CI).
methods or add-ons to the clinical visit. We propose that these clusters should be used to a larger extent in both primary and specialist care for better planning of follow-up and healthcare utilisation. This needs to be investigated in further studies, including health economic evaluation.

Declaration of interest

SG reports personal fees from Roche, outside the submitted work. SW reports grants from GlaxoSmithKline, outside the submitted work. BS reports personal fees from AstraZeneca, personal fees from Novartis, personal fees from Boehringer Ingelheim, personal fees from GlaxoSmithKline, personal fees from Meda, personal fees from TEVA, personal fees from Chiesi, all outside the submitted work. KL reports personal fees from Novartis, personal fees from AstraZeneca, personal fees from BoehringerIngelheim, personal fees from GlaxoSmithKline, personal fees from Chiesi, all outside the submitted work. GB reports personal fees from Astra Zeneca, personal fees from Amgen, personal fees from Boehringer-Ingelheim, personal fees from Chiesi, personal fees from AstraZeneca, personal fees from Novartis, personal fees from Sanofi, personal fees from Teva, all outside the submitted work. All other authors have no conflicts of interest to disclose with regard to the present work.

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L. Lahousse http://orcid.org/0000-0002-3494-4363

References