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The importance of cardiovascular disease for mortality in patients with COPD: a prognostic cohort study

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Background. Cardiovascular diseases are the major cause of mortality in patients with chronic obstructive pulmonary disease (COPD), however, are rarely considered in prediction models in patients with COPD.

Objective. To quantify the effect of cardiovascular determinants on mortality in patients with a GP's diagnosis of COPD.

Methods. Four hundred and five patients aged ⩾65 years with a diagnosis of COPD (244 with COPD by spirometry) were followed up for an average period of 4.2 (SD 1.4) years. Cox proportional hazard regression analyses with bootstrapping techniques were performed to identify independent predictors of all-cause mortality.

Results. In multivariable analysis, all-cause mortality was best predicted by age [hazard ratio (HR) 1.05 [95% confidence interval (CI): 1.01–1.10] per year of age], angina pectoris on history taking [HR 2.32 (95% CI: 1.50–3.58)], airflow obstruction [HR 1.02 (95% CI: 1.01–1.03) per percentage decrease in level of forced expiratory volume in one second (FEV_1) as % predicted] and C-reactive protein [HR 1.04 (95% CI: 1.02–1.05] per milligram per millilitre increase), respectively. The final model had a C statistic of 0.78 (95% CI: 0.72–0.83) after bootstrapping, and the calibration of the model was very good. The model performed similarly in the subgroup of 244 patients with COPD according to the GOLD criteria (post-dilatory FEV_1/forced vital capacity < 0.70).

Conclusions. Physicians should consider ischaemic heart disease in the clinical evaluation of any patient with a GP's diagnosis of COPD. Angina pectoris on history taking is a strong predictor of all-cause mortality in these patients and should be treated adequately to improve prognosis.

Keywords. Cardiovascular disease, COPD, prediction, prognosis.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by incompletely reversible limitation in airflow and is a major cause of morbidity and mortality.[1] COPD is the fourth leading cause of death in the USA and it is predicted to be the third most frequent cause of death in the world by 2020.[2,3]

In previous studies, several predictors of mortality in patients with COPD were identified, e.g. age,[4–7] dyspnoea (functional breathlessness),[8] body mass index (BMI),[5] history of cardiovascular disease,[5] C-reactive protein,[9,10] the forced expiratory volume in one second (FEV_1)[4,5,9] and the ratio of inspiratory capacity (IC) to total lung capacity (TLC), the IC/TLC.[11] Most previous studies evaluated single predictors, without multivariable analysis or building a prognostic model. In 2004, a multidimensional grading system—the BODE index (BMI, airflow obstruction as measured by FEV_1, functional dyspnoea and exercise capacity)—was proposed as a prognostic model in patients with COPD.[8] Although the discrimination power (C statistic) was good (0.74), application of the BODE index in clinical practice is limited by the 6-minute walk test. Recently, this shortcoming was underscored by others who proposed a prognostic index with age, degree of dyspnoea and airflow obstruction [age, dyspnoea, and airflow obstruction (ADO)

index, a model with comparable prediction after external validation as the BODE index].[12] The BODE and ADO indexes, as other previous prognostic models, were derived from and validated in patients from hospital care and thus included mainly severely affected patients with COPD.[4,8,9,12–14] Previous studies underscored the fairly low discrimination ability of the updated BODE and ADO indexes in other cohorts of COPD patients, and authors suggested that important predictors, such as coexisting cardiovascular disease, are still missing in both indexes,[12] realizing that cardiovascular co-morbidities are known as major cause of death and are common, although not always recognized, in patients with COPD.[2,15]

Importantly, prognostic models derived from secondary care with more severely affected patients cannot be straightforward applied in the primary care setting where less severely affected patients are managed. A prognostic model or adequate assessment of prognostic predictors in primary care patients with COPD is lacking. This is an important shortcoming because nowadays the majority of patients with COPD in the USA and Western Europe are predominantly managed by GPs in primary care.[16,17]

For the primary care setting, it is important to assess prognostic determinants in 'all' patients with COPD, including both patients with a clinical diagnosis, as well as with a diagnosis of COPD according to the GOLD criteria [the ratio of the post-bronchodilatory FEV_1 and forced vital capacity (FVC) < 70%].[2] Knowledge of the most important prognostic predictors in such a primary care population of patients with COPD would be very helpful to guide the GP in the patient management, including the comprehensive treatment of these patients.

We therefore evaluated determinants, including cardiovascular ones as possible prognostic factors for all-cause mortality in our cohort of patients aged ⩾65 years with a GP's diagnosis of COPD.

Methods

Study population

The study cohort consisted of 405 patients with a GP's diagnosis of COPD, aged ⩾65 years, who were in a clinically stable condition at the time of investigations. Patients were recruited from 51 general practices in The Netherlands between April 2001 and June 2003.[18] In the sample of general practices, inner-city, urban, suburban and rural communities are represented, reflecting the patient population of general practices in The Netherlands. COPD was diagnosed by the GP when (i) patients had symptoms of dyspnoea, cough or sputum production for at least 3 months/year in two consecutive years or (ii) patients had aforementioned symptoms and a post-dilatory FEV_1/FVC <0.7. In total, 1716 patients had a GP's diagnosis of COPD. Patients known with a diagnosis of heart failure established by a cardiologist (n = 98) and patients with serious psychiatric diseases, severe immobility or terminal illness (n = 432) were excluded for the assessment. Patients known with an established diagnosis of heart failure were excluded because in the original study, we intended to establish the prevalence of previously undetected heart failure.[19] Of the remaining 1186 eligible patients, 781 patients refused to participate. All 405 participants (34% of the eligible patients) underwent extensive pulmonary function testing, including spirometry to assess whether they had COPD according to the GOLD criteria. Information on symptoms, smoking history and medication use was obtained by a standardized questionnaire, including the Rose questionnaire to assess symptoms suggestive of angina pectoris on history taking.[20] Additionally, participants received electrocardiography, chest radiography, blood testing [including measurements of B-type natriuretic peptides (NTproBNP and C-reactive protein)] and echocardiography.[18]

Between February and June 2007, follow-up data, including vital status (date and cause of death when died) were obtained for all but one case who was lost to follow-up. Follow-up data were obtained by scrutinizing the GP's electronic medical files, including letters from specialists.[21] All patients in The Netherlands are registered with one GP, and every health-care worker is obliged to inform the GP about the death of a person. We are convinced of complete capture of all deaths in our cohort.

The Institutional Review Board of the University Medical Center Utrecht, The Netherlands, approved the study protocol, and all participants gave written informed consent.

Variables selection

No straightforward method exists to estimate the required number of patients for studies aiming to quantify the independent contribution of each prognostic test studied. We restricted ourselves to 12, partly overlapping, potentially predictive variables known from literature (Appendix 1).[4–11,22–26] We assessed the following variables known from literature in 405 participants at baseline between April 2001 and June 2003: age,[4–7] sex,[24] angina pectoris on history taking, a history of ischaemic heart disease,[4] the degree of dyspnoea,[8] BMI,[5,8] FEV_1,[4,5] IC,[22] TLC,[9,11] C-reactive protein,[10] abnormal electrocardiography[4] and oral corticosteroid intake.[25]

Data analysis

To evaluate the differences in patient characteristics between patients with established COPD according to the GOLD criteria and patients with only a clinical

diagnosis, the Mann–Whitney *U*-test and chi-square test were used, as appropriate.

Univariable Cox regression analysis was utilized to quantify the relation between the aforementioned possible prognostic variables and all-cause mortality. Variables with a *P* value <0.15, based on the likelihood ratio test, were considered as potential predictors. The potential predictors were included in a multivariable stepwise backward Cox regression analysis to determine the independent contribution to all-cause mortality. Four factors, i.e. age, angina pectoris on history taking, FEV_1 as percentage of predicted value and C-reactive protein, had the strongest association and remained in the final maximally reduced model. C statistics was used to estimate the discrimination power of the model, i.e. the ability to distinguish patients at risk of death from those who are not.[27]

Sixteen subjects had in total 22 missing values. To minimize bias introduced by missing data, we performed single imputation of missing values with SPSS 14.0 (SPSS Software, Chicago, IL).[28]

Results of any model will be too optimistic if the model is applied to the same dataset from which it was developed.[28] To take over-fitting into account and internally validate the model, random bootstrapping techniques were utilized to calculate a shrinkage factor using S-PLUS 6.1 (Insightful Corp, Seattle, WA).[28]

With a calibration plot, we compared the 5-year survival probability predicted by the final model with the observed probability of survival in our cohort. For this, we divided the patients into eight subgroups of 50 subjects on average, each with a comparable observed survival probability and each representing a survival class.

To produce an easy applicable scoring system, based on the absolute risks of 5-year mortality of individual patients, the continuous variables of the final model were digitomized. Regression coefficients after bootstrapping were divided by the smallest coefficient and rounded off to the nearest integer. This yielded points for each predictor. A nomogram was produced to help GPs to quantify the 5-year mortality risk of individual patients (Fig. 3).

We made a Kaplan–Meier plot for all-cause mortality of the four GOLD stages as measure of severity of COPD. The log-rank test was used to evaluate the statistical significance.

The final model was validated in the subpopulations of 244 patients with established COPD according to the GOLD criteria and in 161 patients with only a clinical diagnosis of COPD.

We also applied the BOD index (the BODE index but without the 6-minute walking test) and the ADO index to our study population and calculated the C statistics of these models. We used the BOD index because the 6-minute walk test is seldom assessed in clinical practice in primary or secondary care.

Results

At entry, the study population had a median age of 72 years (Inter Quartile Range 8 years), a mean BMI of 26.7 kg/m^2 (SD 4.2) and 55% were male. In total, 244 (60%) patients fulfilled the GOLD criteria for COPD, with 80 (32.8%), 119 (48.8%), 44 (18.0%) and 1 (0.4%) patients in GOLD Stages I–IV, respectively. GOLD Stages I–IV were defined as FEV_1 as % predicted >80%, 50–80%, 30–50% and <30% of the predicted value, respectively.[2]

Baseline characteristics of the participants are shown in Table 1. Patients with a clinical diagnosis of COPD were <1.2 years and had significantly more often hypertension than those with established COPD according to the GOLD criteria. In all participants, ischaemic heart disease was common (20.2%) as were other cardiovascular diseases.

TABLE 1 *Characteristics of 405 included patients with COPD according to whether they fulfilled the GOLD criteria*

Characteristics	All participants (*n* = 405)	COPD GOLD (*n* = 244)	COPD clinical (*n* = 161)	*P* value
Median (IQR) age (years)	72 (8)	73 (7)	72 (9)	0.03
Male	223 (55.1)	167 (68.4)	56 (34.8)	<0.001
Ischaemic heart disease[a]	82 (20.2)	53 (21.7)	29 (18.0)	0.36
Hypertension	145 (35.8)	74(30.3)	71 (44.1)	0.005
Diabetes mellitus	42 (10.4)	21 (8.6)	21 (13.0)	0.15
Stroke/TIA	21 (5.2)	11 (4.5)	10 (6.2)	0.45
Atrial fibrillation	34 (8.4)	22 (9.0)	12 (7.5)	0.58
Valvular disease	14 (3.5)	11 (4.5)	3 (1.9)	0.15
Heart failure with LVEF < 45%	42 (10.4)	27(11.1)	15 (9.3)	0.57
Heart failure with LVEF ⩾ 45%	41 (10.1)	23 (9.4)	18 (11.2)	0.57
Other pulmonary diseases[b]	100 (24.8)	71 (29.2)	29 (18.0)	0.01
Angina pectoris on history taking[c]	74 (18.3)	50(20.5)	24 (14.9)	0.16
Oral corticosteroid intake[d]	20(4.9)	17(7.0)	3(1.9)	0.02
Also treated by a cardiologist	66 (16.3)	45 (18.4)	21 (13.0)	0.15
Also treated by a pulmonologist	143 (35.3)	108 (44.3)	35 (21.7)	<0.001

Values represent numbers (percentages) unless stated otherwise. COPD GOLD: post-dilatory FEV_1/FVC < 70%; COPD clinical: a clinical diagnosis of COPD, without spirometric data. IQR, inter quartile range; TIA, transient ischaemic attack; LVEF, left ventricular ejection fraction.

[a]History of ischaemic heart disease includes a history of myocardial infarction, angina pectoris, percutaneous coronary intervention or coronary artery bypass grafting.

[b]Other pulmonary diseases includes asthma, lung malignancy, tuberculosis, bronchiectasis, pulmonary embolism, pulmonary restriction, one-sided diaphragm paralysis and sarcoidosis.

[c]Angina pectoris on history taking at the initial investigation (April 2001 to June 2003).

[d]Five to 10 mg/day for >3 months/year.

Participants were followed up for a mean period of 50 (range 0.07–73) months, except one patient who was completely lost to follow-up. During the follow-up period, 60 (14.9%) patients died. From the electronic medical files of the GPs, we could extract that 20 (33.3%) patients died from cardiovascular events, 12 (20%) from respiratory diseases, 13 (21.7%) from cancer (five of lung cancer) and 15 (25%) from other causes of death.

The univariable association between potential predictors and mortality is shown in Table 2. All selected potential predictors, except oral corticosteroid intake, were related to all-cause mortality ($P < 0.15$ as criterion).

After multivariable stepwise backward Cox regression analysis with P value <0.10 as criterion, age [hazard ratio (HR) 1.05 (95% CI: 1.01–1.10) per year of age], angina pectoris on history taking [HR 2.32 (95% CI: 1.50–3.58)], airflow obstruction [HR 1.02 (95% CI: 1.01–1.03) per percentage decrease in level of FEV_1 as % predicted] and C-reactive protein [HR 1.04 (95% CI: 1.02–1.05) per milligram per millilitre increase] remained independent predictors of mortality and they constituted the final maximally reduced model (Table 3). The shrinkage factor of this model was rather high (0.83) with bootstrapping techniques and the C statistic of the final reduced model after applying the shrinkage factor was 0.78 (95% CI: 0.72–0.83).

When the final model was applied to the patients with COPD according to GOLD criteria (n = 244) within the cohort, the C statistic was 0.74 (95% CI: 0.67–0.80), while the C statistic was 0.81 (95% CI: 0.70–0.92) in the remaining 161 patients with a clinical diagnosis of COPD within the cohort who not conformed to the GOLD criteria of COPD, that is, who had a post-dilatory $FEV_1/FVC > 0.70$. The prediction of the model in the subgroup of 143 patients who were co-treated by a pulmonologist was also good (C statistic 0.76, 95% CI: 0.67–0.85).

The BOD index had a HR to predict all-cause mortality of 1.46 (95% CI: 1.27–1.68) and a C statistic of 0.66 (95% CI: 0.59–0.73). The recent advocated ADO index (age, degree of dyspnoea, FEV_1)[12] performed similarly to the BOD index in our population with a HR for all-cause mortality of 1.45 (95% CI: 1.25–1.69) and a C statistic of 0.66 (95% CI: 0.59–0.73).

Patients with more severe pulmonary obstruction with spirometry (low FEV_1 as % predicted) had lower survival ($P < 0.001$) than those with less severe obstruction, see Figure 1. The higher the GOLD stage the lower the survival. The survival probability of patients with only a clinical diagnosis of COPD (non-GOLD stage patients) was the best of all the patients in our study.

TABLE 2 *Results of the univariable Cox regression analysis of 404 patients with a diagnosis of COPD*

Potential predictors	HR (95% CI)[a]	P value
Median (IQR) age (years)	1.07 (1.02–1.12)	0.004
Gender (female)	0.60 (0.35–1.02)	0.06
Angina pectoris on history taking[b]	3.57 (1.96–6.50)	<0.001
Ischaemic heart disease[c]	2.02 (1.17–3.49)	0.01
MMRC dyspnoea scale[d]	1.47 (1.20–1.81)	<0.001
Median (IQR) BMI (kg/m^2)	0.94 (0.87–1.01)	0.06
Median (IQR) FEV_1 (% predicted)[e]	0.97 (0.96–0.98)	<0.001
Median (IQR) IC (% predicted)[e]	0.97 (0.96–0.99)	<0.001
Median (IQR) IC/TLC[e]	0.94 (0.92–0.97)	<0.001
Median (IQR) C-reactive protein (mg/l)	1.05 (1.03–1.07)	<0.001
Abnormal electrocardiography[f]	2.01 (1.21–3.33)	0.007
Oral corticosteroid intake	1.44 (0.52–3.99)	0.48

IQR, inter quartile range; MMRC, Modified Medical Research Council.

[a]For continuous variables, the HR have the following meanings. Per percentage decrease in FEV_1 (%), IC (%) and IC/TLC, the risk of all-cause mortality increased by 3%, 3% and 6%, respectively. Per kilogram per square meter increase in BMI, the risk of mortality decreased by 6%. Per milligram per litre increase in serum C-reactive protein levels, the risk of mortality increased by 5%.

[b]Angina pectoris on history taking at the initial investment (April 2001 to June 2003).

[c]History of ischaemic heart diseases includes myocardial infarction, angina pectoris, percutaneous coronary intervention or coronary artery bypass grafting.

[d]The level of dyspnoea was assessed by means of the MMRC Scale.[29] Scores on the MMRC dyspnoea scale can range from 0 to –4, with a score of 4 showing that the patient is too breathless to leave the house or is breathless when dressing or undressing.

[e]Post-dilatory spirometric measurements were used. For predicted values of FEV_1, we used the recommendations of European Respiratory Society.[30] For predicted values of inspiratory capacity, we used the equations generated by Tantucci *et al.*[31]

[f]Suggesting the diagnosis of myocardial infarction (abnormal Q waves), complete or incomplete left bundle branch block, left ventricular hypertrophy, atrial fibrillation, ST and/or T wave abnormalities and sinus tachycardia.

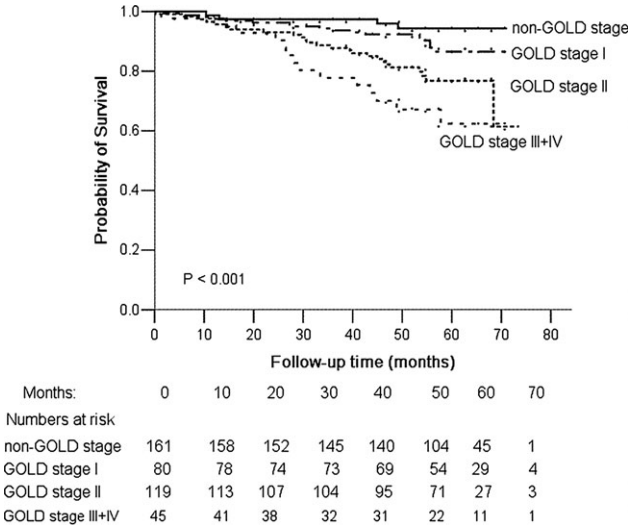
TABLE 3 *Results of the multivariable Cox regression analysis of 404 patients with a diagnosis of COPD*

Variables	HR[a]	95% CI[a]	Regression coefficient[a]	P value[a]	C statistic (95% CI) of model
Age (years)	1.05	1.01–1.10	0.05	0.01	0.78 (0.72–0.83)
Angina pectoris[b]	2.32	1.50–3.58	0.84	<0.001	
FEV_1 (% predicted)	0.98	0.97–0.99	–0.02	<0.001	
CRP (mg/l)	1.04	1.02–1.05	0.04	<0.001	

Data of the final model are presented after correction with the shrinkage factor after bootstrapping. CRP = C-reactive protein.

[a]For the final model, the shrinkage factor after bootstrapping was 0.83.

[b]Angina pectoris on history taking at the initial investment (April 2001 to June 2003).



Months:	0	10	20	30	40	50	60	70
Numbers at risk								
non-GOLD stage	161	158	152	145	140	104	45	1
GOLD stage I	80	78	74	73	69	54	29	4
GOLD stage II	119	113	107	104	95	71	27	3
GOLD stage III+IV	45	41	38	32	31	22	11	1

FIGURE 1 *Kaplan–Meier survival curves for the GOLD stages. GOLD stage is defined as FEV_1/FVC <70%, where Stages I–IV are defined as FEV_1 >80%, 50–80%, 30–50% and <30% of the predicted value, respectively. Non-GOLD stage is defined as FEV_1/FVC >70% (clinical diagnosis of COPD). Survival differed significantly among the four groups (P < 0.001 by the log-rank test)*

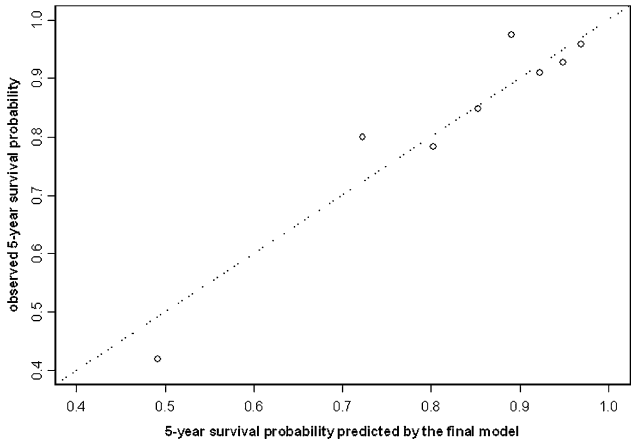


FIGURE 2 *Calibration plot of the final model. The x-axis shows the 5-year probability of survival predicted by the final model and the y-axis the observed survival probability. The patients were divided in eight subgroups of 50 subjects on average, each with a comparable observed survival probability. Every one of the eight circles represents a survival class, with a corresponding predicted and observed survival probability. The dotted line represents perfect agreement between predicted and observed survival probability. Circles above the dotted line show that the predicted survival was lower than the observed probability (underprediction) and circles below the dotted line mean overprediction of the survival probability*

The final model with predicted probabilities matched very well with the observed probabilities of survival over 5 years (good calibration), see also Figure 2. The GP can calculate the absolute 5-year mortality risk of the individual patient with a GP's diagnosis of COPD by applying the simplified scoring system, see Figure 3.

Discussion

Summary of main findings

Angina pectoris on history taking, an abnormal electrocardiogram, and a history of ischaemic heart disease are all, partly overlapping, important prognostic determinants to predict all-cause mortality in patients with a GP's diagnosis of COPD. With age, pulmonary obstruction as measured by FEV_1 as % predicted and the level of C-reactive protein, the easy to obtainable cardiovascular variable 'angina pectoris on history taking' remained in the reduced final model, with a HR to predict all-cause mortality of 2.32 (95% CI: 1.50–3.58%). The predictive value of the final model was at least as good in the subgroup of 161 patients with a clinical diagnosis of COPD, not confirming to the GOLD criteria (C statistic 0.81; 95% CI: 0.70–0.92), as in the 244 patients who did conform to the GOLD criteria (C statistic 0.74; 95% CI: 0.67–0.80).

Strengths and limitations of the study

To the best of our knowledge, this is the first study that extensively evaluated variables related to cardiovascular disease as prognostic determinants in patients with COPD in a multivariable way. Importantly, in a sample of all patients with a GP's diagnosis of COPD. The strength of our study is that the results are applicable to any patient with a GP's diagnosis of COPD, independent of spirometry data. After finishing history taking, physical examination and some exploratory laboratory tests such as C-reactive protein, the GP can calculate an individual 5-year mortality risk of every patient with a GP's diagnosis of COPD with the nomogram (Fig. 3). The calibration of our model was very good, which means that predictions based on the model agreed very well with the 5-year mortality of the patients in our cohort. Our model was internally validated by bootstrapping techniques. A shrinkage factor (0.83 for the final model) was multiplied to the original coefficients to adjust for over-optimism. The high shrinkage factor (close to 1.0) confirms the robustness of our prediction model. Our model predicted mortality also well in the subgroup of 143 patients who were co-treated by a pulmonologist and who were in general more severely affected. Our model would therefore potentially be applicable to patients with COPD managed in secondary care. External validation of our final model, however, is still required before it can be widely used in clinical practice. Unfortunately, we were unable to perform such an externally validation in another existing cohort of patients with COPD simply because other studies that published multivariable models did not consider angina pectoris assessed by history taking or C-reactive protein at baseline.

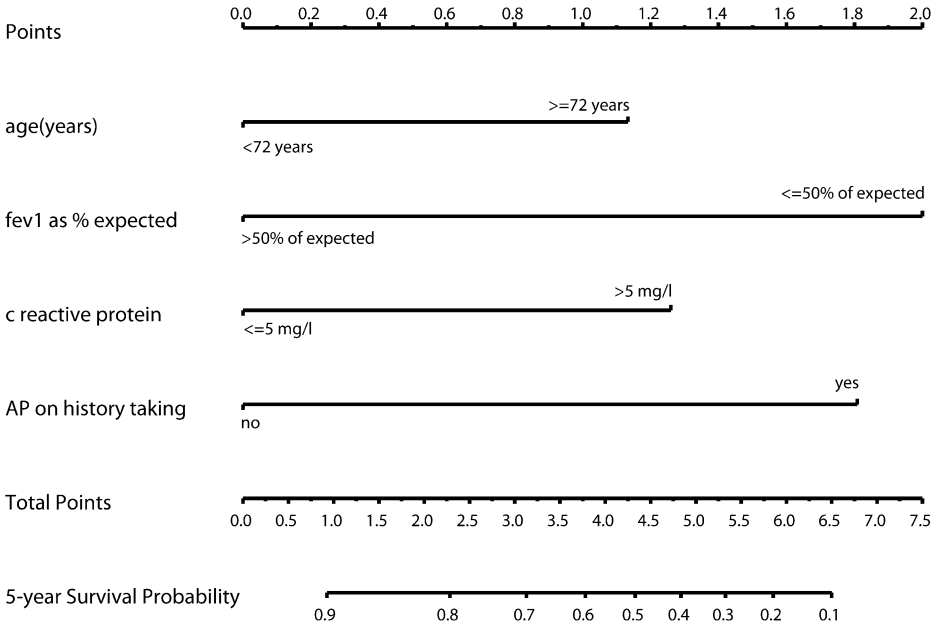


FIGURE 3 *A nomogram to calculate the absolute 5-year survival probability in individuals with a GP's diagnosis of COPD given the values of four predictors. The number of points per predictor can be read from the top line. Total points can be calculated by summing them up. Using the 'Total Points' line as the reference, the absolute probability of survival can be calculated for every individual with a GP's diagnosis of COPD. AP = angina pectoris. An example: A 68-year (0 point)-old patient with COPD, with angina pectoris on history taking (2 points) a FEV_1 of 70% of predicted (0 point) and a plasma C-reactive protein level of 6 mg/ml (1 points) has a score of 3, which is equivalent to an estimated 5-year survival probability of almost 0.72 (the chance of this lady of being alive after 5 years is 72%)*

In our study population, 40% of patients with a GP's diagnosis of COPD patient did not fulfil the GOLD criteria of obstruction with spirometry. Pulmonary function tests are still underused in clinical practice in primary care. Preferably, all patients suspected of COPD should undergo spirometry to improve uniform classification.

In our study population, very severe COPD patients were underrepresented compared to studies that included patients from the hospital setting. This underlines the difference in patient population in primary care as compared to specialist care. It moreover underlines the importance of evaluating prognostic variables in the primary care setting independently from the hospital setting. Moreover, the majority of patients with COPD in the USA and Europe are nowadays mainly managed by the GP in the primary care setting.

Comparison with existing literature

Co-morbidity of cardiovascular disease (including ischaemic heart disease, atrial fibrillation, stroke, peripheral arterial disease, heart failure and valvular disease) in patients with COPD is rather common, with prevalence rates of 38% in the ADO study and 48% in our study.[12] Previous studies showed that cardiovascular determinants could be predictors of all-cause mortality in hospital-based populations.[4,5] A history of cardiovascular diseases and an abnormal electrocardiogram showed to have independent prognostic value.[4,5] In our study, angina pectoris on history taking was the strongest predictor of all-cause mortality, and in the multivariable analysis, it performed better than a history of cardiovascular disease or an abnormal electrocardiogram.

In our study, one-third of the deaths were suspected to be caused by cardiovascular disease, a result comparable with other studies.[32] Irrespective of the knowledge that cardiovascular diseases play an important role in the cause of death of patients with COPD, the most often advocated prognostic models, e.g. the BODE index and the ADO index, did not consider to evaluate cardiovascular co-morbidities as potential predictors. An omission admitted and mentioned in the discussion paragraph by the authors of the ADO study.[5,8,12] Both the BOD and ADO indexes performed rather poor in our study, with a C statistic of 0.66 for both.

In line with previous studies, including the BODE and ADO indexes, the FEV_1 (as % predicted) also showed to be a good predictor of all-cause mortality in our study. The simple measurement of FEV_1 seems to be essential in the evaluation of respiratory decline over time in COPD and is clearly related to the severity of the disease and to the prognosis.[4,5,9,11]

The predictive value of C-reactive protein in COPD is less well established.[9,10] Our results are in line with the study of Man *et al.* They concluded that C-reactive protein measurements would enable accurate detection of patients with COPD at high mortality risk.[10]

However, de Torres *et al.*[9] did not find such a relation. These contrasting results might be caused by differences in patient characteristics. How to interpret C-reactive protein is another problem. It could be regarded as a measurement of systemic inflammation but also as a measure of atherosclerosis. Momentarily, it is unclear which of these two pathways is the main cause for the elevated levels of C-reactive protein in patients with COPD.

Conclusions

In conclusion, our results show that ischaemic heart disease should be considered in all patients with a GP's diagnosis of COPD, irrespective of spirometry results. GPs should ask for chest discomfort compatible with angina pectoris as part of the routine clinical assessment in these patients. Patients with COPD and coexisting angina pectoris should receive established mortality reducing treatment to improve their prognosis. Further research is needed to optimize detection and treatment of (unrecognized) cardiovascular disease in patients with a diagnosis of COPD.

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Declaration

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Conflict of interest: none.

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Appendix 1

Overview of reported risk factors for mortality in patients with COPD (studies from 1997 to 2009)

Characteristic	Independent predictor of mortality	Not an independent predictor of mortality
Age (years)	4–7	
Female sex	24	
Cardiovascular co-morbidity	4,5,32	
Dyspnoea	8	
BMI (kg/m^2)	5,8	23
FEV_1	4,5,8,9	
IC	22	
IC/TLC	9,11	
C-reactive protein (mg/ml)	10	9
Abnormal electrocardiography	4	
Oral corticosteroid intake	25	

Numbers mentioned refer to references.