CHEST

Original Research

COPD

Physical Activity Is the Strongest Predictor of All-Cause Mortality in Patients With COPD

A Prospective Cohort Study

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Background: **Systemic effects of COPD are incompletely reflected by established prognostic assessments. We determined the prognostic value of objectively measured physical activity in comparison with established predictors of mortality and evaluated the prognostic value of noninvasive assessments of cardiovascular status, biomarkers of systemic inflammation, and adipokines.**
Methods: **In a prospective cohort study of 170 outpatients with stable COPD (mean FEV_1, 56% predicted), we assessed lung function by spirometry and body plethysmography; physical activity level (PAL) by a multisensory armband; exercise capacity by 6-min walk distance test; cardiovascular status by echocardiography, vascular Doppler sonography (ankle-brachial index [ABI]), and N-terminal pro-B-type natriuretic peptide level; nutritional and muscular status by BMI and fat-free mass index; biomarkers by levels of high-sensitivity C-reactive protein, IL-6, fibrinogen, adiponectin, and leptin; and health status, dyspnea, and depressive symptoms by questionnaire. Established prognostic indices were calculated. The median follow-up was 48 months (range, 10-53 months).**
Results: **All-cause mortality was 15.4%. After adjustments, each 0.14 increase in PAL was associated with a lower risk of death (hazard ratio [HR], 0.46; 95% CI, 0.33-0.64; $P < .001$). Compared with established predictors, PAL showed the best discriminative properties for 4-year survival (C statistic, 0.81) and was associated with the highest relative risk of death per standardized decrease. Novel predictors of mortality were adiponectin level (HR, 1.34; 95% CI, 1.06-1.71; $P = .017$), leptin level (HR, 0.81; 95% CI, 0.65-0.99; $P = .042$), right ventricular function (Tei-index) (HR, 1.26; 95% CI, 1.04-1.54; $P = .020$), and ABI < 1.00 (HR, 3.87; 95% CI, 1.44-10.40; $P = .007$). A stepwise Cox regression revealed that the best model of independent predictors was PAL, adiponectin level, and ABI. The composite of these factors further improved the discriminative properties (C statistic, 0.85).**
Conclusions: **We found that objectively measured physical activity is the strongest predictor of all-cause mortality in patients with COPD. In addition, adiponectin level and vascular status provide independent prognostic information in our cohort.** ***CHEST 2011; 140(2):331–342***

Abbreviations: ABI = ankle-brachial index; ADO = age, dyspnea, and airflow obstruction; AUROC = area under the receiver operating characteristic; BODE = BMI, airflow obstruction, dyspnea, and exercise capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HR = hazard ratio; hs-CRP = high-sensitivity C-reactive protein; IC/TLC = inspiratory to total lung capacity ratio; MMRC = modified Medical Research Council; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PAL = physical activity level; SGRQ = St. George Respiratory Questionnaire

COPD is an important and growing cause of morbidity and mortality worldwide.[1] It has been characterized as a preventable and treatable disease with significant extrapulmonary effects that may contribute to its severity in individual patients.[2] Cardiovascular, musculoskeletal, metabolic, and mental comorbidities are considered to be part of the frequently prevalent nonpulmonary sequelae of the disease.[3,4] Increasing evidence suggests that extrapulmonary effects of COPD and airflow limitation are only poorly correlated.[5] Prognostic research in COPD has established several assessments beyond airflow limitation: Hyperinflation,[6] reduced exercise capacity,[7,8]

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malnutrition,[9] muscle wasting,[10,11] degree of dyspnea,[12] impaired health status,[8] degree of depressive symptoms,[13] and presence of low-grade systemic inflammation[14,15] were shown to predict mortality in COPD. Furthermore, two multidimensional scores were developed that predict mortality in patients with COPD better than their single components: the BODE (BMI, airway obstruction, dyspnea, and exercise capacity) index[16] and the ADO (age, dyspnea, and airflow obstruction) index.[17]

Physical activity is an important predictor of mortality in healthy subjects[18] and those with several chronic diseases.[19-21] In patients with COPD, physical activity is related to pulmonary limitations[22-24] and extrapulmonary effects of the disease.[25] One epidemiologic study demonstrated that some level of physical activity is associated with a lower risk of mortality in COPD.[26] In that study, physical activity was assessed by a questionnaire, which is subject to misclassification biases.[27] The predictive value of objectively measured physical activity still needs to be determined.

Cardiovascular disease plays an important role in mortality of patients with mild and severe COPD.[28,29] However, no noninvasive assessments of cardiovascular status have been established as predictors of mortality in stable COPD. Furthermore, several systemic biomarkers are considered to be related to disease pathology and inflammatory processes in COPD.[30] Among them, serum levels of high-sensitivity C-reactive protein (hs-CRP) have been demonstrated to be related to mortality,[14,15] but ambiguity remains.[31]

Recently, elevated adiponectin levels have been found in patients with COPD.[32] Elevated adiponectin levels predict mortality in several chronic diseases.[33-36] To our knowledge, the prognostic value of elevated adiponectin levels in COPD has not been studied so far.

The present study aimed to determine the prognostic value of objectively measured physical activity compared with established predictors of mortality and to evaluate the prognostic value of noninvasive assessments of cardiovascular status, biomarkers of systemic inflammation, and adipokines. A secondary aim was to identify the best predictive model of independent risk factors for all-cause mortality.

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Materials and Methods

Study Population

In 2006, 170 stable outpatients with COPD (128 men, 42 women) with GOLD (Global Initiative for Chronic Obstructive Lung Disease) stages I (n = 34), II (n = 57), III (n = 43), and IV (n = 36) were investigated at the Pulmonary Research Institute at Hospital Grosshansdorf, Grosshansdorf, Germany. The patients were enrolled in a prospective observational study to investigate the role of extrapulmonary effects of COPD for disease severity and disease progression. The objective measurement of physical activity had a central role. Patients were recruited from the institute's database that is used for clinical trials in COPD; it consisted of 691 ambulatory patients with COPD (mean FEV_1, 54% predicted; mean age, 62 years). Patients were contacted by a study nurse, and those who expressed their availability and interest in the study were enrolled. Exclusion criteria were an exacerbation of COPD within the past 2 months, clinical signs of acute heart failure, and severe pain syndromes that could interfere with physical activity. Further details on methods and cross-sectional analyses have been described previously.[23,25,37,38] The study was approved by the Ethics Committee of Medical Association Schleswig-Holstein, Bad Segeberg, Germany [III/EK 116/05(I)], and participants gave written informed consent.

Physical Activity

Physical activity was measured by a multisensory armband (SenseWear; BodyMedia; Pittsburgh, Pennsylvania). We assessed the physical activity level (PAL) and step counts per day over a period of 5 to 6 consecutive days for at least 22.5 h a day as previously described.[23,25] Reliability of this assessment period has been shown.[23] PAL was calculated by dividing the total daily energy expenditure by whole-night sleeping energy expenditure.[25] According to the World Health Organization, a PAL of ≥ 1.70 defines an active person, 1.40 to 1.69 defines a sedentary person, and < 1.40 defines a very inactive person.[18,23] Energy expenditure estimates of the multisensory armband have been validated against the doubly labeled water technique in healthy subjects[39] and against indirect calorimetry in patients with COPD.[40,41] Step counts of the armband showed a high correlation ($r = 0.86$) with vector magnitude units derived by another validated accelerometer in 120 patients who wore both devices simultaneously over a period of 5 to 6 days.[42]

Lung Function and Functional Exercise Capacity

Postbronchodilator spirometry (performed 15 min after administration of 400 μg salbutamol) and body plethysmography were used to measure lung function according to current guidelines and established reference values.[43,44] The 6-min walk test was conducted according to current guidelines.[45]

Cardiovascular Status

Cardiac function was assessed by transthoracic echocardiography (Vivid 3; GE Healthcare; Chalfont St Giles, England), and serum levels of N-terminal pro-B-type natriuretic peptide

(NT-proBNP) (Elecsys proBNP Immunoassay; Roche Diagnostics GmbH; Mannheim, Germany) were determined as previously described.[25,38] We measured systolic left-sided heart function (left ventricular ejection fraction), diastolic left-sided heart function (ratio of the peak velocity of the early E-wave to atrial A-wave),[46] and global right ventricular function (Tei index, which is the sum of isovolumetric contraction time and isovolumetric relaxation time divided by the ejection time).[47]

To assess peripheral artery disease, we performed vascular Doppler sonography (SonoMate100; DEGO GmbH; Nagold, Germany) and calculated the ankle-brachial index (ABI) as previously described.[48] ABI was analyzed as a categorized variable. An ABI <1.00 is associated with an increased risk of death in several populations.[49]

Nutritional and Muscular Status

BMI was calculated as weight in kilograms divided by height in meters squared. Fat-free mass was determined by bioelectrical impedance analysis (Nutriguard-M; Data Input GmbH; Darmstadt, Germany) using a recently developed formula.[50] The fat-free mass index was calculated as fat-free mass in kilograms divided by height in meters squared. Muscle depletion was defined as a fat-free mass index <17.05 kg/m^2 in men and <14.62 kg/m^2 in women.[11,50]

Adipokines and Systemic Inflammation

Total serum adiponectin and leptin levels were measured by enzyme-linked immunosorbent assay (R&D Systems; Oxford, England). Hs-CRP (latex assay) (Roche Diagnostics), fibrinogen level (modified method of Clauss),[25] and IL-6 (enzyme-linked immunosorbent assay) (R&D Systems; Minneapolis, Minnesota) were measured according to the manufacturers' instructions.

Questionnaires and Multidimensional Mortality Scores

Dyspnea was assessed by the modified Medical Research Council (MMRC) dyspnea scale. Health-related quality of life was assessed by the St. George Respiratory Questionnaire (SGRQ). The activity subdomain was analyzed separately. Depressive symptoms were measured by the Beck Depression Inventory. Patients were classified according to the criteria of the BODE index,[16] updated BODE index,[17] and ADO index.[17]

Mortality

The outcome of this study was all-cause mortality. Vital status was ascertained by follow-up visits and telephone contacts. The censor date was July 26, 2010. One patient in GOLD stage I was lost to follow-up; therefore, 169 patients were eligible for survival analyses. Date of death was verified by contacting relatives and general practitioners. Survival time was defined as the time of the baseline visit to the date of death or date of the last contact.

Statistical Analyses

Characteristics of survivors and nonsurvivors are presented as mean and SD (normally distributed variables), median and interquartile range (skewed or categorical variables), or number and percent (dichotomous variables). Differences were compared using two-tailed t test for normally distributed variables, Mann-Whitney U test for categorical variables or in the case of heteroscedasticity, and χ^2 tests for dichotomous variables. Skewed variables were log-transformed to normalize the distribution.

The relation of physical activity categories and all-cause mortality was analyzed by Kaplan-Meier survival plots and log-rank tests using established cut points for categorization. To analyze the relative risk of mortality for physical activity as a continuous variable, we used multivariate Cox proportional hazard analyses. To further test for a linear association between physical activity and all-cause mortality, we added quadratic terms for the PAL and steps per day to each model.[18]

To compare the discriminative properties of the prognostic assessments for 4-year survival, we calculated the C statistics for all predictors, which is analogous to the area under the receiver operating characteristic (AUROC) curve. Furthermore, we used multivariate Cox regression analyses to estimate the relative risk of all-cause mortality associated with the prognostic assessments. First, we calculated the crude hazard ratios (HRs) for each variable. Second, to compare the relative risks among the predictors, we divided all continuous variables by a one-half SD to reveal standardized units and adjusted for age and sex (e-Appendix 1).

To identify the best predictive model of mortality, we performed a stepwise multivariate Cox regression with a backward elimination (entry threshold, $P<.05$; removal threshold, $P<.10$) fitted with all candidate variables that were significant predictors at the univariate level. To compare the model fit of the revealed predictors with the model fit of established models (ie, the linear forms of the continuous BODE and ADO predictors), we calculated the –2 log-likelihoods. A lower level of the –2 log-likelihood indicates a better model fit. To compare the discriminative properties of these predictors for 4-year survival with the discriminative properties of the BODE and ADO indexes, we used AUROC curves (e-Appendix 1). To analyze the intermediary impact of established predictors on the relative risk that was associated with the independent predictors of our model, we quantified the attenuation of each HR by adding the potential intermediate predictors in separate Cox regression models (e-Appendix 1). Data analysis was performed with the statistical software SPSS, version 16.0 (SPSS Inc; Chicago, Illinois).

Results

Baseline Characteristics and Survival

Patient characteristics at baseline are shown in Table 1. Twenty-six (15.4%) patients died over a median follow-up of 48 months (range, 10-53 months). There were significant differences between survivors and nonsurvivors in FEV_1, inspiratory to total lung capacity ratio (IC/TLC), PAL, step counts per day, 6-min walk distance, BMI, fat-free mass index, Tei index, NT-pro-BNP, ABI, adiponectin level, degree of dyspnea, SGRQ total score and activity subdomain, and mortality risk scores. Patient medication and comorbidities according to their medical history are shown in e-Table 1.

Association Between Physical Activity and Mortality

The probability of survival differed significantly among the World Health Organization categories of PAL (Fig 1). The absolute risk of 4-year mortality for very inactive, sedentary, and active patients was 31%, 9%, and 0%, respectively. Next, we evaluated the prognostic value of PAL and steps per day as continuous variables. After standardization and adjustment

Table 1—*Patient Characteristics by Survival Status*

Characteristic	Survivors	Nonsurvivors	*P* Value
Description			
Patients	143 (84.6)	26 (15.4)	
Age, y	63.6 (6.6)	66.1 (6.4)	.083
Men	107 (74.8)	20 (76.9)	.82
Current smokers	62 (43.4)	9 (34.6)	.41
Pack-y smoked	52 (26)	52 (20)	.98
Lung function			
FEV_1, % predicted	58.8 (21.1)	41.4 (21.9)	< .001
IC/TLC	34.5 (9.6)	25.2 (11.0)	< .001
Physical activity			
Physical activity level	1.55 (0.27)	1.27 (0.18)	< .001
Steps per day	6424 (3679)	3006 (2081)	< .001
Exercise capacity			
6-min walk distance, m	450 (107)	317 (144)	< .001
Nutritional status			
BMI, kg/m^2	26.7 (5.1)	23.5 (4.3)	.004
Muscular status			
Fat-free mass index, kg/m^2	18.9 (2.6)	17.6 (2.4)	.023
Muscle depletion[a]	13 (9.5)	7 (26.9)	.013
Cardiovascular status			
LVEF ≤ 50%	4 (3)	1 (4)	.79
E-wave/A-wave	0.93 (0.21)	0.88 (0.20)	.32
Tei index	0.41 (0.11)	0.47 (0.15)	.033
NT-proBNP, pg/mL	64 (38-106)	98 (49-209)	.038
ABI	1.02 (0.92-1.11)	0.93 (0.79-1.01)	.012
ABI < 1.00	66 (46)	21 (81)	.001
Adipokines			
Adiponectin, ng/mL	5649 (3,998-8,689)	9042 (3,402-19,453)	.039
Leptin, ng/mL	7348 (3,325-14,898)	5548 (1,902-10,555)	.057
Systemic inflammation			
hs-CRP, mg/L	2.8 (1.2-6.3)	2.9 (1.1-5.6)	.96
IL-6, pg/mL	2.8 (1.7-4.9)	3.0 (1.5-6.2)	.68
Fibrinogen, mg/dL	431 (96)	462 (105)	.13
Questionnaires			
MMRC grade	2 (1-3)	3 (2-4)	.002
SGRQ (total score)	43 (20)	54 (20)	.014
SGRQ (activity score)	56 (24)	70 (19)	.004
Beck Depression Inventory	7 (3-13)	7 (3-12)	.74
Mortality scores			
BODE index	2 (0-3)	4 (2-7)	< .001
Updated BODE index	1 (0-3)	6 (2-10)	< .001
ADO index	3 (2-4)	5 (4-6)	< .001

Variables that were normally distributed are presented as mean (SD) and were tested by two-tailed *t* test or, in case of heteroscedasticity (steps per day), by Mann-Whitney *U* test. Skewed variables are presented as median (interquartile range) and were tested log-transformed. Categorized variables are presented as median (interquartile range) and were tested by Mann-Whitney *U* test. Dichotomous variables are presented as No. (%) and were tested by χ^2 test. Data were missing for fat-free mass index and muscle depletion (n = 5), LVEF (n = 3), E-wave/A-wave (n = 8), Tei index (n = 24), and leptin level (n = 7). ABI = ankle-brachial index; ADO = age, dyspnea, and airflow obstruction; BODE = BMI, airflow obstruction, dyspnea, and exercise capacity; hs-CRP = high-sensitivity C-reactive protein; IC/TLC = inspiratory to total lung capacity ratio; LVEF = left ventricular ejection fraction; MMRC = modified Medical Research Council; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SGRQ = St George Respiratory Questionnaire.

[a]Muscle depletion was defined as fat-free mass index < 17.05 kg/m^2 in men and < 14.62 kg/m^2 in women.

for age and sex, each one-half SD increase in PAL (0.14) and steps per day (1,845) was associated with a lower risk of death (HR, 0.46; 95% CI, 0.33-0.64; $P < .001$, and HR, 0.49; 95% CI, 0.35-0.69; $P < .001$, respectively) (Table 2). There was no evidence of a curvilinear association when quadratic terms were added (PAL squared, $P = .75$; steps per day squared, $P = .71$).

Comparison of the Prognostic Value of Physical Activity With Established Predictors

Table 2 presents the results of the C statistic analyses (AUROC curve) and the Cox regression analyses (crude and adjusted HRs). The C statistic revealed the PAL to have the best ability to distinguish between survivors and nonsurvivors (AUROC curve, 0.81), followed by steps per day (AUROC curve, 0.80).

Table 2—*Prognostic Value of Physical Activity and Established Predictors of Mortality in Patients With COPD*

	C Statistic	Crude Cox Regression of the Raw Predictors			Adjusted Cox Regression of the Standardized Predictors[a]		
	AUROC	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Lung function							
FEV_1, %	0.75	0.96	0.94-0.98	< .001	0.56	0.41-0.75	< .001
IC/TLC	0.75	0.91	0.87-0.95	< .001	0.59	0.46-0.75	< .001
Physical activity							
Physical activity level	0.81	0.005	0.001-0.050	< .001	0.46	0.33-0.64	< .001
Steps per day	0.80	0.9996	0.9994-0.9998	< .001	0.49	0.35-0.69	< .001
Exercise capacity							
6-min walk distance, m	0.77	0.993	0.990-0.996	< .001	0.63	0.53-0.75	< .001
Nutritional and muscular status							
BMI, kg/m^2	0.68	0.87	0.79-0.96	.003	0.67	0.52-0.86	.002
Fat-free mass index, kg/m^2	0.64	0.82	0.70-0.97	.022	0.61	0.45-0.83	.001
Systemic inflammation							
Log hs-CRP, mg/L	0.51	0.98	0.62-1.56	.94	1.00	0.82-1.21	.98
Questionnaires							
MMRC grade	0.68	1.63	1.20-2.22	.002	1.28	1.10-1.49	.002
SGRQ (total score)	0.64	1.02	1.00-1.04	.018	1.38	1.11-1.72	.004
SGRQ (activity score)	0.67	1.03	1.01-1.05	.006	1.45	1.15-1.83	.002
Log Beck Depression Inventory	0.50	1.08	0.70-1.66	.73	1.07	0.87-1.32	.51
Mortality scores							
BODE index	0.76	1.44	1.24-1.66	< .001	1.47	1.26-1.71	< .001
Updated BODE index	0.75	1.24	1.14-1.35	< .001	1.26	1.15-1.38	< .001
ADO index	0.77	1.76	1.37-2.25	< .001	1.76	1.37-2.25	< .001

Values were missing for fat-free mass index (n = 5). AUROC = area under the receiver operating characteristic; HR = hazard ratio. See Table 1 legend for expansion of other abbreviations.

[a]HRs were adjusted for age and sex, except the HR of the ADO index. The ADO index was adjusted for sex only. For standardization, all continuous variables were divided by one-half SD. The MMRC grade was standardized by multiplying by 2.

After adjustment for age and sex, highly significant ($P < .001$) HRs were observed for PAL, steps per day, FEV_1, IC/TLC, 6-min walk distance test, BODE index, updated BODE index, and ADO index. Significant ($P < .01$) HRs were observed for BMI, fat-free mass index, MMRC dyspnea grade, and SGRQ (total score and activity subdomain). Categorizing predictors with established cut points (ie, BMI < 21 kg/m^2, fat-free mass index < 14.62 kg/m^2 in women and < 17.05 kg/m^2 in men, hs-CRP > 3.0 mg/L, and Beck Depression Inventory score ≥ 15) did not improve the associations (data not shown). The highest relative risk of death was observed for a standardized decrease in PAL (117%), followed by steps per day (104%) (Fig 2). The comparison of the independent prognostic value of physical activity with those of FEV_1, IC/TLC, 6-min walk distance, BMI, fat-free mass index, MMRC, and SGRQ total score when included simultaneously in different multivariate Cox regression analyses showed the superiority of physical activity (Table 3).

Evaluation of Further Potential Predictors of Mortality

The predictive values of cardiac function, peripheral vascular status, adipokines, IL-6 level, and fibrinogen level for all-cause mortality are shown in Table 4. After adjustment for age and sex, Cox regression analyses revealed a higher Tei index, higher serum adiponectin levels, lower serum leptin levels, and an ABI < 1.00 to be significantly associated with a higher risk of all-cause mortality (Table 4).

Best Model of Independent Predictors of Mortality

In a stepwise multivariate Cox regression model, PAL, adiponectin level, and ABI < 1.00 were the best independent predictors of mortality (Table 5). This model revealed a better model fit than did those with the linear forms of the continuous BODE and ADO index predictors (–2 log-likelihood, 210, 224, and 235, respectively). C statistic analyses revealed PAL, adiponectin level, and ABI < 1.00 to have better discriminative properties than the BODE and ADO indexes (AUROC curve, 0.85, 0.76, and 0.75, respectively) (Fig 3).

Next, we analyzed the attenuation of the adjusted HRs that were associated with each independent predictor by adding potential intermediate factors (e-Table 2), one at a time, in separate Cox regression models (e-Table 3). The HR associated with PAL was only partly attenuated by FEV_1, IC/TLC, MMRC, or 6-min walk distance (e-Table 3). The largest, but still small, attenuation (28.6%) was observed when FEV_1, MMRC, and 6-min walk distance were added

Table 3—*Different Multivariate Cox Regression Models Comparing the Independent Prognostic Value of Physical Activity With Those of Established Predictors of Mortality*

Paired Variables	Multivariate Cox Regressions[a] HR	95% CI	*P* Value	Paired Variables	Multivariate Cox Regressions[a] HR	95% CI	*P* Value
FEV_1, per 11% predicted	0.74	0.54-1.03	.071	FEV_1, per 11% predicted	0.72	0.52-1.01	.058
Physical activity level, per 0.14[b]	0.55	0.39-0.79	.001	Steps per day, per 1,845	0.60	0.42-0.88	.008
IC/TLC, per 5.2%	0.73	0.57-0.95	.017	IC/TLC, per 5.2%	0.72	0.56-0.92	.010
Physical activity level, per 0.14	0.55	0.39-0.78	.001	Steps per day, per 1,845	0.59	0.41-0.84	.003
6-min walk distance, per 61 m	0.76	0.62-0.94	.010	6-min walk distance, per 61 m	0.76	0.59-0.96	.023
Physical activity level, per 0.14	0.58	0.41-0.83	.003	Steps per day, per 1,845	0.66	0.45-0.98	.041
BMI, per 2.6 kg/m^2	0.75	0.58-0.98	.033	Body-mass index, per 2.6 kg/m^2	0.70	0.55-0.90	.006
Physical activity level, per 0.14	0.50	0.36-0.69	< .001	Steps per day, per 1,845	0.51	0.37-0.70	< .001
Fat-free mass index, per 1.3 kg/m^2	0.71	0.52-0.99	.043	Fat-free mass index, per 1.3 kg/m^2	0.63	0.46-0.87	.005
Physical activity level, per 0.14	0.50	0.36-0.69	< .001	Steps per day, per 1,845	0.49	0.35-0.68	< .001
MMRC grade, per 0.5 grade	1.07	0.90-1.27	.44	MMRC grade, per 0.5 grade	1.03	0.86-1.23	.78
Physical activity level, per 0.14	0.49	0.34-0.69	< .001	Steps per day, per 1,845	0.51	0.34-0.74	.001
SGRQ total score, per 10 points	1.05	0.81-1.36	.70	SGRQ total score, per 10 points	1.02	0.78-1.34	.88
Physical activity level, per 0.14	0.48	0.33-0.69	< .001	Steps per day, per 1,845	0.50	0.34-0.74	.001

Values were missing for fat-free mass index (n = 5). See Table 1 and 2 legends for expansion of abbreviations.

[a]Fourteen different multivariate Cox regression analyses are presented, each adjusted for age and sex. For standardization, all predictors were divided by one-half SD.

[b]Replacing the physical activity level by SGRQ activity score revealed an HR of 1.12 (95% CI, 0.85-1.48; *P* = .43) for the SGRQ activity score.

simultaneously to the basic model. The HR associated with adiponectin level was partly attenuated (35.5%) after IC/TLC and fat-mass index were added to a basic model, which was adjusted for age, sex, history of diabetes, homeostatic model assessment index, and levels of triglycerides, high-density lipoproteins, leptin, and hs-CRP. The HR associated with ABI < 1.00 was attenuated by 43.6% after FEV_1 and 6-min walk distance was added. In a subgroup analysis that included patients in GOLD stages I to III only, the mortality risk associated with ABI was higher than the risk in the total cohort and was only attenuated by 24.2% when FEV_1 and 6-min walk distance were added (e-Table 3).

Discussion

The main finding of our study is that objectively measured physical activity is the best predictor of all-cause mortality in patients with COPD. In addition, higher levels of adiponectin and an impaired vascular status provide independent prognostic information in our cohort.

Physical Activity

Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure beyond resting energy.[51] Physical activity has been shown to be an important predictor of mortality in healthy subjects[18] and in those with several chronic diseases.[19-21] The physiologic processes underlying the relationship between physical activity and survival are complex and only incompletely understood. It has been speculated that physical inactivity leads to dysregulated cellular and molecular circuitry, which directly contributes to multiple chronic health disorders.[52] For COPD, there is only one epidemiologic study that addressed the relationship between physical activity and mortality during a mean follow-up of 12 years.[26] Subjects with airflow obstruction who reported a very low level of physical activity on a questionnaire had a higher risk of death than those who reported higher levels of physical activity.[26] However, such observations must be interpreted with caution because questionnaire-based assessments of physical activity are subject to misclassification biases,[27] typically overestimate absolute amounts of physical activity,[53,54] and do not provide accurate estimates of absolute amounts of activity per day.[18,54] In the present study, we show that objectively measured physical activity is a strong predictor of mortality in patients with COPD. Furthermore, we found a linear association between physical activity and mortality. For every 0.14 decrease in PAL, the relative risk of death more than doubled. A 0.14 decrease in PAL

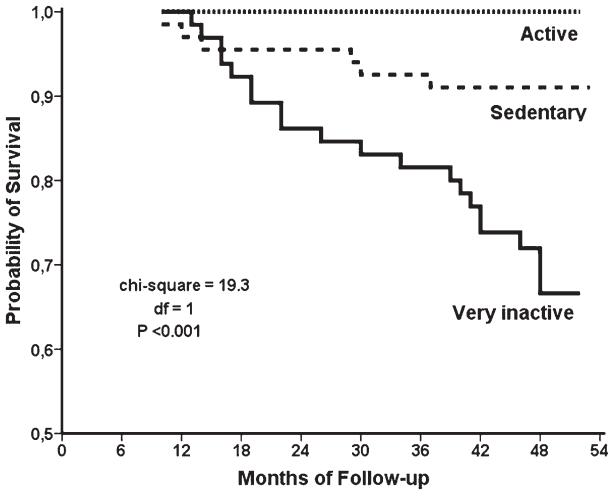

FIGURE 1. Kaplan-Meier survival curves according to World Health Organization categories of physical activity level (PAL). A higher 4-year risk of mortality was observed for sedentary patients (PAL, 1.40-1.69 [dashed line]; log-rank $P = .002$) and very inactive patients (PAL < 1.40 [solid line]; log-rank $P < .001$) than for active patients (PAL ≥ 1.70 [dotted line]). Number of deaths and corresponding total number of patients per category were 20 and 65, respectively, for very inactive patients; 6 and 67, respectively, for sedentary patients; and 0 and 37, respectively for active patients. df = degrees of freedom.

corresponded to a decrease of 200 to 250 kcal in active daily energy expenditure. Compared with other prognostic assessments in our cohort, PAL was the best predictor of all-cause mortality: It revealed the best discriminative properties, had the highest relative risk of mortality per standardized decrease, and remained the strongest independent predictor in a stepwise Cox regression model. We speculate that increasing physical activity in daily life in patients with COPD by interventional programs as shown before[55] might have an impact on mortality risk, which, however, has to be demonstrated by future studies.

Adipokines, Cardiovascular Status, and Mortality

Adipokines, such as adiponectin and leptin, are secreted by the white adipose tissue.[56] They are involved in inflammatory processes, immune response, lipid metabolism, insulin sensitivity, vascular homeostasis, angiogenesis, and regulation of energy balance.[56] Decreased circulating concentrations of adiponectin are associated with obesity, the metabolic syndrome, insulin resistance, and cardiovascular disease.[57] By contrast, serum levels of adiponectin are elevated in the presence of autoimmune diseases and chronic inflammatory conditions, such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, type 1 diabetes, and cystic fibrosis.[58] Furthermore, higher levels of adiponectin have been reported to predict mortality in healthy elderly persons,[59] in patients with chronic heart failure,[33] and in patients with chronic renal failure.[34] Little is known about the role of adipokines in patients with COPD. Expression of adiponectin and leptin by bronchial epithelial cells in COPD have been described.[60,61] A smaller cross-sectional study has demonstrated that serum concentrations of adiponectin are elevated in patients with stable COPD when compared with healthy control subjects.[32] Furthermore, both leptin and adiponectin are associated with the systemic inflammatory process during exacerbations of COPD.[62] In the present study, we show that a higher level of adiponectin and a lower level of leptin are associated with an increased risk of mortality in patients with COPD. However, the prognostic value of adiponectin level was superior and independent of leptin level, sex, lipid metabolism, insulin resistance, systemic inflammation, and fat mass.

The spectrum of the cardiovascular sequelae in patients with COPD includes generalized atherosclerosis, right ventricular dysfunction, and left ventricular diastolic dysfunction.[25,63,64] The ABI is a reliable measure of peripheral arterial disease,[48] is an indicator of generalized atherosclerosis,[65] and improves cardiovascular risk prediction in the general population beyond traditional risk factors.[65] An ABI < 1.00 is associated with an increased risk of death in healthy elderly persons and in several patient populations.[49] In the present study, we found that an impaired ABI is a significant predictor of mortality in patients with COPD. However, the ABI appears to provide better prognostic information for patients in earlier stages of the disease. Furthermore, we found that the Tei index predicts mortality in our study population. The Tei index provides information about global right ventricular function independent of mean pulmonary artery pressure and correlates with stroke volume on right heart catheterization.[47,66] Reduced right ventricular stroke volume has been posited to be related to the degree of emphysema, hyperinflation, and left ventricular filling impairment in patients with COPD.[67,68]

Best Model of Independent Predictors

PAL, adiponectin level, and ABI are independent predictors of the best model of mortality in COPD. No lung function variable remained an independent predictor in the final model. The model fit of the final predictors was better than the model fit of BMI, airflow obstruction, dyspnea, and exercise capacity and of age, dyspnea, and airflow obstruction. Furthermore, PAL, adiponectin level, and ABI revealed a better ability to distinguish between survivors and nonsurvivors than did the BODE and ADO indexes. One possible explanation for the superiority of this model is that it covers several important systemic aspects of the disease: the cardiovascular sequelae, metabolic

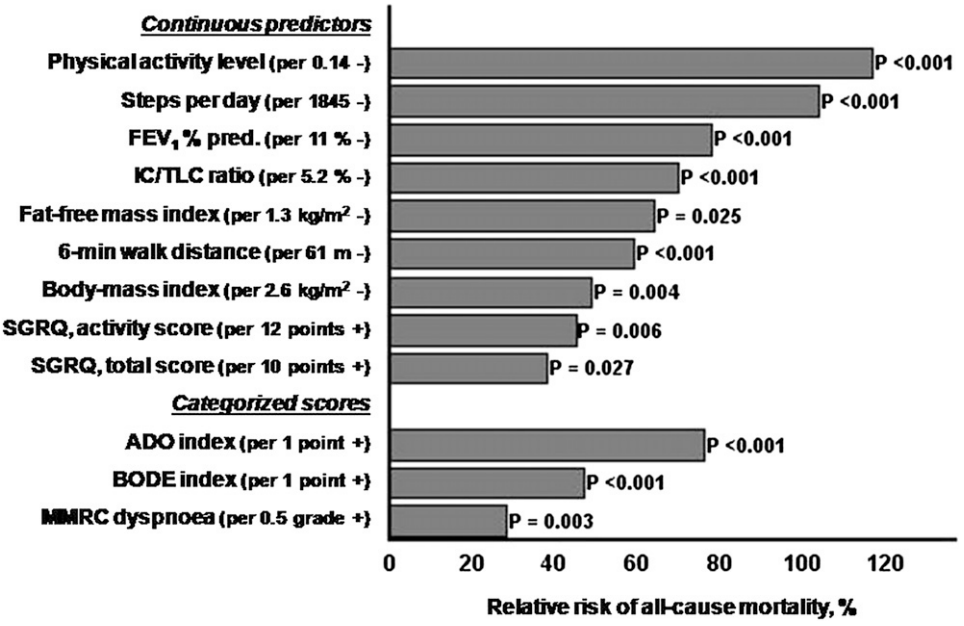

FIGURE 2. Comparison of the relative risk of death associated with physical activity and established predictors of mortality. After adjustment for age and sex, the relative risk was calculated for each one-half SD increase (+) or decrease (–) in continuous predictors and for each 1-point increase in categorized scores. The ADO index already includes the effect of age and was adjusted for sex only. MMRC dyspnea grade was multiplied by 2. All predictors were distributed within a range of 9 to 11 integral numbers or score points. The relative risk of mortality was calculated from hazard ratios (HRs) shown in Table 2 as follows: for HRs < 1.00, $[(1/HR)-1] \times 100\%$; for HRs > 1.00, $(HR-1) \times 100\%$. Values were missing for fat-free mass index (n = 5). ADO = age, dyspnea, and airflow obstruction; BODE = BMI, airway obstruction, dyspnea, and exercise capacity; IC/TLC = inspiratory to total lung capacity ratio; MMRC = modified Medical Research Council; SGRQ = St. George Respiratory Questionnaire.

alterations, and physical inactivity as the integral of several organ dysfunctions. Furthermore, these markers partly capture the effect of other established predictors of mortality, such as lung function impairment, exercise intolerance, and body composition.

Established Predictors of Mortality

Highly significant predictors with good discriminative properties in our study were the 6-min walk distance, FEV_1, and IC/TLC, all of which have been

Table 4—*Prognostic Value of Potential Predictors of Mortality in Patients With COPD*

	C Statistic	Crude Cox Regression of the Raw Predictors			Adjusted Cox Regression of the Standardized Predictors[a]		
	AUROC	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Cardiovascular status							
E-wave/A-wave	0.56	0.35	0.04-3.43	.36	0.93	0.74-1.17	.53
Tei-index[b]	0.61	1.48	1.06-2.06	.021	1.26	1.04-1.54	.020
Log NT-proBNP, pg/mL	0.62	1.47	1.05-2.06	.027	1.16	0.97-1.39	.12
ABI	0.66	0.16	0.04-0.70	.015	0.85	0.72-0.99	.041
ABI < 1.00		4.34	1.64-11.52	.003	3.87	1.44-10.40	.007
Adipokines							
Log adiponectin, ng/mL	0.63	1.99	1.07-3.69	.029	1.34	1.06-1.71	.017
Log leptin, ng/mL	0.59	0.71	0.51-0.99	.044	0.81	0.65-0.99	.042
Systemic inflammation							
Log IL-6, pg/mL	0.51	1.12	0.70-1.80	.64	1.05	0.86-1.27	.66
Fibrinogen, mg/dL	0.60	1.003	0.999-1.006	.14	1.13	0.96-1.33	.15

Values were missing for E-wave/A-wave (n = 8), Tei index (n = 24), and leptin level (n = 7). See Table 1 and 2 legends for expansion of abbreviations.

[a]HRs were adjusted for age and sex. For standardization, all continuous variables were divided by one-half SD.

[b]The raw Tei index was multiplied by 10 to get a useful HR.

Table 5—*Best Model of Independent Predictors of All-Cause Mortality Revealed by a Stepwise Multivariate Cox Regression Analyses*

	Regression Coefficient	SE	HR	95% CI	*P* Value
Physical activity level	−4.718	1.148	0.009	0.001-0.085	< .001
Log adiponectin, ng/mL	0.825	0.333	2.28	1.19-4.38	.013
ABI < 1.00	1.182	0.504	3.26	1.22-8.75	.019

Model fit: –2 log-likelihood = 210; $\chi^2 = 39.4$; degrees of freedom = 3; $P < .001$; N = 169. There were some missing values in the initial stepwise Cox regression; therefore, the remaining significant predictors of the stepwise model (physical activity level, adiponectin level, and ABI) were analyzed again in a separate multivariate Cox regression without missing values, which is given in this table. See Table 1 and 2 legends for expansion of abbreviations.

shown to be relevant predictors of mortality in patients with COPD.[6-8] Furthermore, airways obstruction, hyperinflation, and functional exercise capacity have been shown to be important physiologic variables related to physical activity in patients with COPD.[22,23] Accordingly, we found that these measurements partly contributed to the increased risk of mortality that is associated with decreased physical activity.

The BODE index was developed in patients with severe to very severe COPD as a prognostic index that includes information about BMI, airflow obstruction, dyspnea, and exercise capacity.[16] The BODE index has been demonstrated to be a better predictor of mortality than airflow obstruction[16] and hyperinflation.[6] The present study confirms these observations.

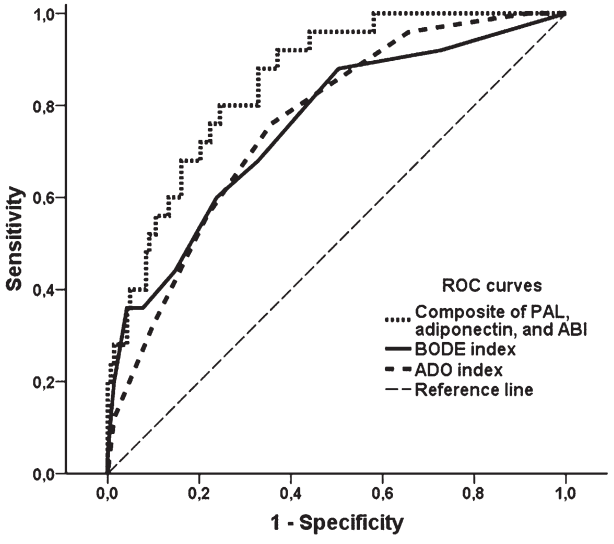

FIGURE 3. Receiver operating characteristic curves for the BODE index, the ADO index, and the composite of PAL, adiponectin level, and ABI as predictors of mortality in patients with COPD. The corresponding areas under the curves for the composite of PAL, adiponectin level, and ABI; the BODE index; and the ADO index were 0.85, 0.76, and 0.75, respectively. ABI = ankle-brachial index. See Figure 1 and 2 legends for expansion of other abbreviations.

Because of poor calibration of the BODE index in two external cohorts, Puhan and coworkers[17] updated the BODE index. However, the updated BODE index did not improve the discriminative ability in their cohort, which suggests that important predictors are still missing. In line with the findings of Puhan et al,[17] we were unable to demonstrate an improvement in the discriminative properties of the updated BODE index in our cohort. Furthermore, Puhan and coworkers developed the ADO index as a simplified risk score for primary care. In the present study, the ADO index showed good discriminative properties and a large increase in the mortality risk per 1-point increase. The strength of the ADO index is that it is driven by age, which is the most important determinant of survival independent of disease diagnosis.[69]

In the present study, we evaluated the predictive power of several other established prognostic factors in patients with COPD, including malnutrition,[9,70-72] muscle wasting,[10,11] systemic inflammation,[14,15] health status,[8] the degree of depressive symptoms,[13] and dyspnea.[12] We confirmed that muscle wasting and malnutrition are significant determinants of mortality. However, their predictive properties were inferior to measures of physical activity, exercise capacity, and lung function. We did not find an association between mortality and levels of hs-CRP or other markers of systemic inflammation. Hs-CRP level was shown to predict mortality in two epidemiologic studies of COPD[14,15] but showed no association with mortality in another COPD cohort.[31] Health status[8] and the degree of dyspnea[12] have been found to be independent predictors of mortality in patients with COPD. In the present study, we confirm the prognostic properties of health status and the MMRC dyspnea scale, but these predictors had a prognostic value inferior to that of the physiologic measures in our cohort. Of interest, in our study population, the activity subdomain of the SGRQ had a better prognostic value than the total score but was inferior to objectively measured physical activity. Furthermore, when replacing objectively measured physical activity by SGRQ activity score in a model adjusted for FEV_1, the SGRQ activity score no longer remained an independent predictor of mortality. The degree of depressive symptoms has been found to predict mortality in patients with severe to very severe COPD.[13] The present study population covered the whole spectrum of disease severity and had, on average, a lower score on the Beck Depression Inventory; we did not observe an impact of depression on mortality in our cohort.

Study Limitations and Conclusions

Our study has some limitations. First, the total number of deaths in our study was low, which is a potential source of bias. However, resulting HRs and C statistics for established predictors showed similarities with the results in larger COPD cohort studies, for example: (1) in Celli et al,[16] the BODE index HR was 1.34 (95% CI, 1.26-1.42) and C statistic, 0.74, vs the present cohort HR of 1.44 (95% CI, 1.24-1.66) and C statistic of 0.76; (2) in Casanova et al,[6] the IC/TLC C statistic was 0.74, vs the present cohort C statistic of 0.75; and (3) in Oga et al,[8] SGRQ activity score HR was 1.04 (95% CI, 1.02-1.06) vs the present cohort HR of 1.03 (95% CI, 1.01-1.05). Therefore, it is unlikely that our results are biased by the low number of deaths. Second, a selection bias has to be considered because our patients were recruited from the institute's database, which consists of patients who also participate in clinical studies. Therefore, one might assume that the frequency of comorbid conditions in the cohort might be less than the frequency of comorbid conditions in other COPD populations. However, patients of our cohort had similar frequencies of comorbidities according to their medical history when compared with recently reported data of other cohorts.[73,74] Therefore, it is not likely that a selection bias explains the observed results. Third, losses to follow-up are a main cause of selection bias in longitudinal studies. In our study, only one patient was lost to follow-up.

In conclusion, we found that objectively measured physical activity is the best predictor of mortality compared with a broad range of other prognostic assessments in patients with COPD. Furthermore, we identified adiponectin level, leptin level, vascular status, and echocardiographically assessed right ventricular dysfunction to be novel predictors of mortality. PAL, adiponectin level, and vascular status provided the best independent prognostic information for patients with COPD. The current findings need to be confirmed in larger COPD cohorts.

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Author contributions: Dr Waschki had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Dr Waschki: contributed to the data collection, statistical analysis, and data interpretation and wrote the first draft of the manuscript.
Dr Kirsten: contributed to the data collection and interpretation and revision of the manuscript.
Dr Holz: contributed to the data collection and interpretation and revision of the manuscript.
Dr Müller: contributed to the data collection and interpretation and revision of the manuscript.
Dr Meyer: contributed to the statistical analysis, data interpretation, and revision of the manuscript.
Dr Watz: contributed to the study design, the data collection and interpretation, and writing of the manuscript.
Dr Magnussen: contributed to the study design, data interpretation, and writing of the manuscript.
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Additional information: The e-Appendix and e-Tables can be found in the Online Supplement at http://chestjournal.chestpubs.org/content/140/2/331/suppl/DC1.

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