Biological Research for Nursing
2018, Vol. 20(4) 429-439

DOI: 10.1177/1099800418772346
journals.sagepub.com/home/brn
SAGE

Mortality in Advanced Chronic Obstructive Pulmonary Disease and Heart Failure Following Cardiopulmonary Rehabilitation

Youjeong Kang, PhD, MPH, CCRN[1], Bonnie G. Steele, PhD, ARNP[2], Robert L. Burr, PhD, MSEE[3], and Cynthia M. Dougherty, PhD, ARNP[2,3]

Abstract

Cardiopulmonary rehabilitation (CR) improves physical function and quality of life (QoL) in chronic obstructive pulmonary disease (COPD) and heart failure (HF), but it is unknown if CR improves outcomes in very severe disease. This study's purpose was to describe functional capacity (6-min walk distance [6MWD], steps/day), symptoms (dyspnea, depression), QoL (Short-Form Health Survey–Veterans [SF-36 V]) and cardiopulmonary function (*N*-terminal pro-brain natriuretic peptide [NT-proBNP], forced expiratory volume in 1 s [FEV_1]), and derive predictors of mortality among patients with severe COPD and HF who participated in CR. **Methods and Results:** In this secondary analysis of a randomized controlled trial comparing two CR methods in severe COPD and HF, 90 (COPD = 63, HF = 27) male veterans, mean age 66 $\pm$ 9.24 years, 79% Caucasian, and body mass index 31 kg/m^2, were followed for 12 months after CR. The COPD group had greater functional decline than the HF group (6MWD, $p = .006$). Dyspnea was lower ($p = .001$) and QoL higher ($p = .006$) in the HF group. Mean NT-proBNP was higher in the HF group at all time points. FEV_1 improved over 12 months in both groups ($p = .01$). Mortality was 8.9%, 16.7%, and 37.8% at 12, 24, and 60 months, respectively. One-year predictors of mortality were baseline total steps (<3,000/day), 6MWD (<229 meters), and NT-proBNP level (>2,000 mg/pg). **Conclusions:** In very severe COPD and HF, risks of mortality over 12 months can predict patients unlikely to benefit from CR and should be considered at initial referral.

Keywords

mortality, COPD, heart failure, cardiac rehabilitation, pulmonary rehabilitation

In the United States, chronic obstructive pulmonary disease (COPD) and heart failure (HF) are among the top four leading causes of death (Li, Caughey, & Johnston, 2014; Osthoff, Jenkins, & Leuppi, 2013). The incidence of these diseases, both of which are incurable and chronic, is increasing (American Heart Association, 2016; American Lung Association, 2016). Although exacerbations are preventable and treatable with pharmacologic and nonpharmacologic interventions, both diseases are associated with significant morbidity and mortality (American Lung Association, 2016; Carson et al., 2015; Duncan, 2016; Singh & Yu, 2016). Although the trajectories of disease progression differ, symptoms and disability characteristics of HF and COPD are similar at the end of life (Gavazzi et al., 2015). Patients with COPD or HF frequently suffer from the incapacitating symptoms of shortness of breath, fatigue, and weakness. Consequently, both groups have profoundly impaired functional capacity in walking, activities of daily living, and quality of life (QoL; Apostolovic et al., 2011; Li et al., 2014; Padeletti, Jelic, & LeJemtel, 2008; Troosters et al., 2016). These bothersome symptoms cause significant physical and psychological distress that is related to mortality (Janssen, Spruit, Uszko-Lencer, Schols, & Wouters, 2011).

In the past two decades, research has identified similarities in the pathophysiological and functional concomitants of COPD and HF (Louvaris & Vogiatzis, 2015). For this reason, investigators are increasingly aware of the value of applying the traditional cardiopulmonary rehabilitation (CR) model to the management of both HF and COPD (Troosters & VanRemoortel, 2009). Exercise- and activity-based interventions to improve physical functioning and disease self-management in COPD and HF populations improve exercise performance, dyspnea, daily activity, illness exacerbation, QoL, and health-care costs (McCarthy et al., 2015; Tzanis et al., 2016). Recently,

[1] University of Utah School of Nursing, Salt Lake City, UT, USA
[2] Health Services Research and Development, VA Puget Sound Health Care System, Seattle, WA, USA
[3] Biobehavioral Nursing and Health Informatics, University of Washington School of Nursing, Seattle, WA, USA

Corresponding Author:
Cynthia M. Dougherty, PhD, ARNP, School of Nursing, University of Washington, 1959 NE Pacific Street, Box 357266, HSB T615A, Seattle, WA 98195, USA.
Email: cindyd@uw.edu

exercise-based rehabilitation programs have shown promise in the reduction of mortality in HF (Sagar et al., 2015), though similar benefits for COPD are less evident (McCarthy et al., 2015). The effect of such programs on symptoms and mortality in advanced disease, however, remains to be determined. This issue is particularly relevant to CR management because persons with very severe, end-stage HF and/or COPD comprise a high proportion of those referred to CR.

In order to impact survival and determine the efficacy of interventions that may reduce mortality, it is important to identify risk factors for mortality among patients with COPD and HF (Khazanie et al., 2015). Selected indicators, including the 6-min walk distance (6MWD), forced expiratory volume in 1 s (FEV_1), and natriuretic peptides (*N*-terminal pro-brain natriuretic peptide [NT-proBNP]), show promise for predicting mortality in both groups (Fonarow, 2012; Gaggin & Januzzi, 2013; Nunez et al., 2016; Richter et al., 2013; Singh & Yu, 2016). Similarly, reduced physical activity, defined by the World Health Organization as "any force exerted by skeletal muscles that results in energy expenditure above resting level" (Cavill, Kahlmeier, & Racioppi, 2006), is associated with increased risk of mortality in the elderly and those with cardiopulmonary illness (Waschki et al., 2015).

The present analysis was prompted by the findings of our previous randomized controlled trial comparing two forms of outpatient CR in patients in very severe HF or COPD (Steele, Dougherty, Burr, Gylys-Colwell, & Hunziker, 2017). In that study, we found no benefit in functional capacity (6MWD), daily activity (accelerometer), symptoms (dyspnea), or QoL (Short-Form Health Survey–Veterans [SF-36 V]) following outpatient CR. These results suggested that CR interventions in severe end-stage COPD or HF may have little ability to impact outcomes. Furthermore, it is likely that the lack of benefit in very ill subjects is also associated with mortality, rendering CR a less optimal choice. The purpose of the present secondary analysis was to (1) describe functional capacity, symptoms, and QoL by diagnostic group (severe COPD vs. HF) and by mortality group over time following participation in CR and (2) derive predictors of mortality among patients with very severe COPD and HF following participation in CR.

Method

Design of Parent Study

The purpose of the parent study was to compare functional capacity and daily activity outcomes between a standard 8-week outpatient CR program and a 4-week outpatient/home-based self-efficacy-based rehabilitation program. The results at 6 months (Steele et al., 2017) demonstrated that neither form of CR was successful in improving any of the outcomes, and in some instances, functional capacity and daily activity declined during the year after completion of CR in both COPD and HF. Because neither form of CR resulted in significant benefits in either diagnostic group, we combined all patients into one sample for the current analysis.

Setting, Participants, and Interventions

We recruited participants between 2009 and 2012 from the VA Puget Sound Health Care System, Seattle, WA. We randomly assigned outpatients (HF: $n = 27$ or COPD: $n = 63$) to one of the two intervention groups when they met the following criteria: optimally managed, severe COPD (FEV_1 predicted $< 50\%$) or HF with reduced ejection fraction (HF*r*EF; EF $< 40\%$), one disease-related hospitalization in the past 2 years or at least two unscheduled outpatient visits over the past year related to cardiopulmonary disease, a working phone, and willingness to participate in an outpatient exercise and self-management program. Exclusion criteria were unstable disease or recent surgery that precluded exercise, a supplemental oxygen requirement at rest of >4 L/min, already exercising 3 times a week, inability to ambulate, uncontrolled mental illness, alcohol or drug abuse, or a life expectancy of less than 1 year. Participants provided written informed consent, and the VA Research and Development and Human Subjects Committees Institutional Review Board at the VA Puget Sound Health Care System approved the trial. An independent data and safety monitoring board provided oversight for procedures, protocol, and events. We carried out randomization and preprogram (Time 1) measures prior to beginning the CR programs. A team member blinded to group assignment completed postprogram measures.

CR Interventions

The two CR programs we tested were based on social cognitive theory, incorporating concepts of self-efficacy and self-regulation. Briefly, the 4-week outpatient CR adherence program consisted of an outpatient/home-based program of 4 hr of exercise and integrated self-management education weekly, followed by 5 months of weekly phone calls encouraging home exercise for 30 min 3×/week ($n = 46$). Standard outpatient CR consisted of 8 weeks of 2 hr of exercise and self-management instruction weekly ($n = 44$). Outpatient exercise sessions in both groups began with 5 min of upper- and lower extremity stretching, followed by walking on a treadmill for a goal of 20 min and exercise on the NuStep for 20 min at a pace that reached a Borg rating of 3–5 (moderate to strenuous). Following the aerobic exercise, there were 5 min of free arm weights and 5 min of arm ergometry. A 5-min cooldown consisting of upper- and lower extremity stretching concluded each session. All outpatient exercise sessions were monitored using blood pressure, telemetry (heart rate and arrhythmias), and O_2-saturation monitoring. The number of minutes and type of aerobic activity was individually prescribed and was based on the baseline 6MWD.

Following the 8 weeks of standard CR, we gave patients a pedometer to track steps/day and encouraged them to walk 30 min 3×/week. Following the 4-week outpatient phase for the adherence intervention, we completed a home safety evaluation. We asked patients to walk for 30 min 3×/week, record walking sessions in an exercise log, and self-monitor symptoms

and were followed them with weekly coaching phone calls for 3 months to help them maintain exercise after the outpatient program. For the final 2 months of this program, we made biweekly coaching phone calls and asked participants to record home walking and self-monitor symptoms.

Outcome Measures

Primary outcomes in the parent study included functional capacity measured by (1) 6MWD in meters (best of two walks; Cavanaugh, Coleman, Gaines, Laing, & Morey, 2007) and (2) daily physical activity (total steps/24 hr) measured using the StepWatch® Activity Monitor (SAM; Orthocare Innovations, LLC), a pager-sized device worn above the dominant ankle that records stride cycles. Participants wore the SAM for a minimum of 10 hr for a least 5 consecutive days. The measure used from the SAM was total steps taken during 10 hr worn (stride counts doubled; Haeuber, Shaughnessy, Forrester, Coleman, & Macko, 2004; Nguyen, Burr, Gill, & Coleman, 2011). Secondary outcomes were symptoms of dyspnea (Clinical COPD Questionnaire; van der Molen et al., 2003) and depressed mood (Geriatric Depression Scale; Watson & Pignone, 2003), general health-related QoL-Veterans version (SF-36 V; Boueri, Bucher-Bartelson, Glenn, & Make, 2001; Kazis et al., 1998; Sprenkle, Niewoehner, Nelson, & Nichol, 2004), and cardiopulmonary function [NT-pro-BNP; Jelic & Le Jemtel, 2006] and FEV_1 [Miller et al., 2005]). Measures were taken at (1) baseline (study entry), (2) 6 months, and (3) 12 months.

We determined mortality by reports taken from the electronic health record (EHR) from study entry through 60 months following randomization or when we discovered that a patient had died. We noted causes of death from the EHR.

Analysis (Present Study)

To describe the longitudinal trajectories of functional capacity, symptoms, and QoL in the two diagnostic groups (COPD or HF) and the "mortality groups" (dead vs. alive), longitudinal generalized estimating equations (GEEs) controlling for baseline age, body mass index (BMI), and Charlson comorbidity index were used (Charlson, Pompei, Ales, & MacKenzie, 1987). Adjusted standardized odds ratios for potential risk factors for mortality were estimated using univariate logistic regression. Standardized variables were employed to enhance comparability because the scales of the logistic regression coefficients, and hence the estimated odds ratios, depended on the scales of the independent variables in the model. In addition, because the variable NT-proBNP typically has a non-normal right-skewed statistical distribution, it was log-transformed prior to standardization using a Tukey-bias natural logarithm transform (LnNT − proBNP = Ln(1 + NT-proBNP)).

Empirical multivariate models predicting mortality at 12, 24, and 60 months were developed based on the previously described univariate analyses. Potential risk factors for mortality were entered into a multivariate logistic regression model using a forward stepwise procedure. The robust Eicker–Huber–White "sandwich" estimator and the autoregressive lag 1 form for the initial working covariance matrix were specified for the GEE model. Because this was a secondary analysis, we interpret statistical significance at the $p \leq .05$ level conservatively.

Results

Patient Characteristics

There were a total of 90 participants, two thirds of whom had a primary diagnosis of COPD. The mean age for the total group was 66 ± 9.24 years, 79% of participants were Caucasian, the average BMI was 31 kg/m^2, more than half had a college degree or higher, and all were male veterans (Table 1). There were statistically significant differences between the COPD and HF groups in age (COPD > HF), oxygen use (COPD > HF), NT-proBNP level (HF > COPD), and FEV_1 (COPD < HF). The percentage of COPD patients with severe and very severe symptoms (GOLD stages III and IV) was significantly higher than that of patients with HF. There were 12 patients with a diagnosis of HF*r*EF who also had an initial baseline FEV_1 < 50% predicted. Mortality across both groups was 8.9% at 12 months, 16.7% at 24 months, and 37.8% at 60 months. The COPD group had higher mortality at all time points compared to the HF group, with the exception of 24 months.

Outcomes by Diagnostic Group

Participants with COPD had significantly greater functional decline compared to those with HF as indicated by the 6MWD ($p = .006$; Table 2). Those with HF had higher 6MWD at baseline study entry and experienced an increase in 6MWD at 6 months following CR. Those with HF reported lower levels of dyspnea symptoms and higher physical composite scores on the SF-36 V, but these were not significantly different between the groups. Self-reported SF-36 V mental composite scores were comparable to other COPD and HF samples and were low in both groups. Although the score on the physical function subscale of the SF-36 V was lower in the COPD group than in the HF group across all time points, physical function improved at 6 months in both COPD and HF groups ($p = .04$). The mean level of NT-proBNP was higher in the HF group than the COPD group at all time points and declined in the HF group over time ($p = .02$). FEV_1 showed a significant improvement over 12 months in both groups ($p = .02$).

Predictors of Mortality

Risk factors for mortality at 12, 24, and 60 months for the entire sample (Table 3) showed that baseline total steps/24 hr, 6MWD, and log NT-proBNP level were significantly associated with mortality at all time periods in both COPD and HF groups. At 12 months, the odds of death were higher for those with a higher dyspnea score and lower self-efficacy for exercise, SF-36 V physical function, and SF-36 V general health. At 24 months, additional predictors of mortality were FEV_1, SF-

Table 1. Baseline Demographic and Clinical Characteristics (Mean ± *SD* or *n* [%]).

Characteristic	Total ($N = 90$)	COPD ($n = 63$)	HF ($n = 27$)	p (D × Gp)
Age (years)	66.0 ± 9.24	67.3 ± 9.43	63.0 ± 8.17	.03
Race				.53
Caucasian	71 (78.9)	49 (77.8)	22 (81.5)	
African American	14 (15.6)	10 (15.9)	4 (14.8)	
Asian/Pacific Islander	3 (3.3)	2 (2.2)	1 (1.1)	
Hispanic	1 (1.1)	1 (1.1)	0	
American Indian	1 (1.1)	1 (1.1)	0	
BMI (kg/m^2)	31.2 ± 7.46	30.7 ± 7.06	32.4 ± 8.35	.37
Education				.36
Elementary school	5 (5.6)	5 (7.9)	0 (0)	
High school	32 (35.6)	24 (38.1)	8 (29.6)	
College/tech school	47 (52.2)	30 (47.6)	17 (63.0)	
Graduate school	6 (6.7)	4 (6.3)	2 (7.4)	
Marital status				.31
Never married	9 (10.0)	6 (9.5)	3 (11.1)	
Married/partnered	27 (30.0)	22 (34.9)	5 (18.5)	
Separated, divorced, widowed	54 (60.0)	35 (55.6)	19 (70.4)	
Employment status				.42
Paid employment	12 (13.3)	10 (15.9)	2 (7.4)	
Unemployed	7 (7.8)	4 (6.3)	3 (11.1)	
Disabled	33 (36.7)	25 (39.7)	8 (29.6)	
Retired	38 (42.2)	24 (38.1)	14 (51.9)	
Oxygen use	43 (47.8)	39 (61.9)	4 (14.8)	<.001
Current smoker	24 (26.7)	16 (25.4)	8 (29.6)	.79
Charlson score	2.17 ± 1.20	2.05 ± 1.11	2.44 ± 1.37	.19
EF% (HF group only)	30.9 ± 6.68		30.9 ± 6.68	
NT-proBNP	1,086.3 ± 2,013.6	468.6 ± 900.9	2,527.5 ± 2,977.0	.001
FEV_1	39.8 ± 11.3	32.2 ± 12.3	57.7 ± 19.2	<.001
GOLD staging				<.001
Stage I: FEV_1 > 80%	4 (4.4)	0 (0.0)	4 (14.8)	
Stage II: FEV_1 > 50% and < 80%	17 (18.9)	6 (9.5)	11 (40.7)	
Stage III: FEV_1 > 30% and < 50%	40 (44.4)	31 (49.2)	9 (33.3)	
Stage IV: FEV_1 < 30%	29 (32.2)	26 (41.3)	3 (11.1)	

Note. The *p* values reported for the continuous variables are based on independent groups. Student's *t*-test (unequal variance formula) was used to contrast the COPD and HF groups. The *p* values reported for the categorical variables are based on a general (R×C) Fisher's exact test. BMI = body mass index; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; FEV_1 = forced expiratory volume in 1 s; HF = heart failure; NT-proBNP = *N*-terminal pro-brain natriuretic peptide; *SD* = standard deviation.

36 V physical function, and the dyspnea score. At 60 months, the same factors that were strong predictors of mortality at both 12 and 24 months continued to be statistically significant, with the addition of self-efficacy for walking.

In the multivariate logistic regression model for the entire sample (Table 4), COPD Dyspnea Scale scores and self-efficacy for walking were predictive of death at 12 months. Similarly, FEV_1 and log NT-proBNP were predictive of death at 24 months, and total steps/24 hr and log NT-proBNP were predictive of death at 60 months. The Nagelkerke R^2 was 0.65 at 12 months, 0.40 at 24 months, and 0.47 at 60 months. The percentage correctly classified was 94.4% at 12 months, 85.6% at 24 months, and 82.2% at 60 months.

Outcomes by Mortality Groups

The trajectories in functional capacity, QoL, symptoms, and self-efficacy by mortality groups (Table 5) demonstrate that four variables differed significantly between the survivors and nonsurvivors over 12 months. These included baseline levels of dyspnea symptoms ($p = .04$), mental health ($p = .02$), self-efficacy for walking ($p = .05$), and FEV_1 ($p = .03$).

Discussion

The parent intervention study compared two forms of CR and demonstrated that those with very severe COPD or HF experienced few benefits in functional capability, symptoms, and QoL following participation in CR. These findings are in stark contrast with the CR literature that demonstrates clear benefit in these outcomes in less severe disease (Fleg et al., 2015; McCarthy et al., 2015). In general, those with COPD in the present study had worse outcomes than those with HF. In both groups, however, there were three consistent risk factors for mortality across the 60-month study period: lower baseline 6MWD and total steps/day and higher NT-proBNP levels. Our

Table 2. Functional Capacity, Symptoms, and Quality of Life: Baseline and 6 and 12 Months, by Diagnostic Group.

	Time Point			Wald χ^2		*p* Value	
Variable	Baseline (Mean ± *SD*)	6 Months (Mean ± *SD*)	12 Months (Mean ± *SD*)	Group[a]	Group × Time[b]	Group[a]	Group × Time[b]
Functional capacity							
6MWD (m)				3.68	10.37	.05	.006
Total	354.69 ± 117.39	343.17 ± 113.89	314.29 ± 131.29				
COPD	339.21 ± 115.82	317.06 ± 123.52	302.77 ± 129.66				
HF	390.82 ± 115.12	407.82 ± 139.54	343.08 ± 134.24				
Total steps/24 hr				0.22	2.33	.64	.31
Total	5,337.27 ± 3,053.33	5,244.92 ± 3,120.11	5,327.01 ± 3,324.02				
COPD	5,065.39 ± 2,668.28	5,145.79 ± 3,174.35	5,185.51 ± 3,237.43				
HF	5,971.66 ± 3,786.54	5,522.48 ± 3,024.71	5,680.72 ± 3,593.27				
Symptoms							
Dyspnea				15.92	3.51	<.001	.17
Total	3.02 ± 1.40	2.69 ± 1.36	2.85 ± 1.58				
COPD	3.29 ± 1.22	3.13 ± 1.12	3.16 ± 1.43				
HF	2.39 ± 1.60	1.54 ± 1.25	2.13 ± 1.70				
Quality of life (SF-36 V)							
PCS				7.42	4.10	.006	.12
Total	31.96 ± 8.18	32.83 ± 10.26	32.02 ± 10.99				
COPD	30.17 ± 7.47	30.87 ± 8.92	31.14 ± 10.64				
HF	36.13 ± 8.39	37.81 ± 11.91	34.04 ± 11.75				
MCS				0.15	0.76	.70	.68
Total	48.84 ± 11.82	51.47 ± 11.66	50.04 ± 11.53				
COPD	49.35 ± 12.24	51.72 ± 11.29	49.45 ± 12.27				
HF	47.66 ± 10.89	50.87 ± 12.83	51.37 ± 9.73				
Physical Function				7.09	6.19	.008	.04
Total	38.63 ± 20.68	43.53 ± 23.55	41.76 ± 25.00				
COPD	34.76 ± 18.01	37.60 ± 21.43	39.34 ± 24.55				
HF	50.00 ± 22.36	58.36 ± 22.31	47.39 ± 25.66				
General Health				3.07	1.35	.08	.51
Total	46.69 ± 18.41	48.67 ± 20.83	48.85 ± 20.58				
COPD	45.07 ± 18.97	46.29 ± 21.41	48.17 ± 20.65				
HF	50.48 ± 16.76	54.72 ± 18.55	50.56 ± 20.80				
Cardiopulmonary function							
NT-proBNP				14.20	7.33	<.001	.02
Total	1,086.28 ± 2,013.60	727.10 ± 958.32	708.86 ± 1,124.69				
COPD	468.62 ± 900.88	370.93 ± 598.79	452.60 ± 787.30				
HF	2,527.48 ± 2,977.00	1,374.25 ± 1,149.25	1,319.00 ± 1,534.14				
FEV_1				37.32	8.23	<.001	.02
Total	39.85 ± 19.20	41.82 ± 22.35	44.62 ± 20.87				
COPD	32.18 ± 12.30	34.18 ± 14.86	35.81 ± 15.32				
HF	57.74 ± 20.65	61.30 ± 26.51	66.42 ± 16.37				
Self-efficacy							
Self-efficacy exercise				2.09	1.16	.14	.56
Total	6.44 ± 2.33	5.62 ± 2.44	5.28 ± 2.88				
COPD	6.36 ± 2.31	5.58 ± 2.54	4.99 ± 2.81				
HF	6.63 ± 2.40	5.74 ± 2.23	5.94 ± 2.99				
Self-efficacy walking				3.93	4.81	.05	.09
Total	2.88 ± 2.42	3.82 ± 3.07	3.19 ± 2.92				
COPD	2.25 ± 2.04	3.38 ± 2.96	3.11 ± 2.89				
HF	4.14 ± 2.74	4.95 ± 3.24	3.39 ± 3.02				

Note. Total $N = 90$ (COPD: $n = 63$, HF: $n = 27$). 6MWD = 6-min walk distance; COPD = chronic obstructive pulmonary disease; HF = heart failure; FEV_1 = forced expiratory volume in 1 s; MCS = mental component score; NT-proBNP = *N*-terminal pro-brain natriuretic peptide; PCS = physical component score; SF-36 V = Short-Form 36–Veterans version.

[a]Group differences between COPD and HF. [b]COPD and HF Trajectory × Time.

Table 3. Risk Factors for Mortality for Veterans With HF and COPD, Combined, at 12, 24, and 60 Months After Cardiopulmonary Rehabilitation.[a]

Variable	Odds Ratio (95% CI)	*p* Value
At 12 months	Alive: 82; Dead: 8	
Total steps/24 hr	0.35 [0.13, 0.90]	.03
6MWD	0.15 [0.04, 0.55]	<.01
Log NT-proBNP	4.16 [1.43, 12.1]	.01
COPD Dyspnea Scale	3.22 [1.22, 8.53]	.02
Self-efficacy exercise	0.33 [0.12, 0.90]	.03
SF-36 V, physical function	0.28 [0.10, 0.78]	.02
SF-36 V, general health	0.19 [0.05, 0.69]	.01
At 24 months	Alive: 75; Dead: 15	
Total steps/24 hr	0.34 [0.17, 0.70]	.01
6MWD	0.28 [0.13, 0.60]	.01
FEV_1	0.37 [0.17, 0.77]	.01
Log NT-proBNP	2.98 [1.43, 6.19]	.01
COPD Dyspnea Scale	2.45 [1.26, 4.78]	.01
SF-36 V, physical function	.50 [0.26, 0.94]	.03
At 60 months	Alive: 56; Dead: 34	
Total steps/24 hr	0.38 [0.22, 0.66]	<.01
6MWD	0.37 [0.21, 0.66]	<.01
Log NT-proBNP	2.81 [1.58, 4.99]	<.01
Self-efficacy walking	0.50 [0.30, 0.83]	.01

Note. $N = 90$. 6MWD = 6-min walk distance; CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 s; HF = heart failure; Log NT-proBNP = *N*-terminal pro-brain natriuretic peptide; SF-36 V = Short-Form 36–Veterans version.
[a]Controlling for age, body mass index, and Charlson score.

Table 4. Multivariate Predictors of Mortality for Veterans With HF and COPD, Combined, at 12, 24, and 60 Months After Cardiopulmonary Rehabilitation.

Variable	β	*SE*	Wald Z^2	*p* Value
At 12 months				
COPD Dyspnea Scale	1.56	.75	4.33	.04
Self-efficacy walking	−2.61	.99	6.83	<.001
Overall	$\chi^2 = 21.7$, $df = 6$. Nagelkerke $R^2 = .65$			
	Correct classification = 94.4%			
At 24 months				
FEV_1	−1.42	.47	9.06	.003
Log NT-proBNP	1.58	.50	9.76	.002
Overall	$\chi^2 = 24.5$, $df = 5$. Nagelkerke $R^2 = .40$			
	Correct classification = 85.6%			
At 60 months				
Total steps/24 hr	−0.81	.37	4.89	.027
Log NT-proBNP	1.02	.30	7.59	.006
Overall	$\chi^2 = 38.4$, $df = 6$. Nagelkerke $R^2 = .47$			
	Correct classification = 82.2%			

Note. $N = 90$. COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 s; HF = heart failure; NT-proBNP = *N*-terminal pro-brain natriuretic peptide; *SE* = standard error.

findings suggest that those with baseline 6MWD < 229 m, total steps < 3,000/day, or NT-proBNP > 2,000 mg/pg are not likely to benefit from CR or survive beyond 1 year. There were a number of other predictors of mortality that were not the same at 12, 24, and 60 months, but that were related to lower physical capacity at baseline entry into CR. Some of these risk factors are interrelated; for example, 6MWD may be limited by dyspnea in both COPD and HF groups (Troosters et al., 2016).

In the present study, mortality rates in both the COPD and HF groups increased from 8% at 12 months to 34% at 60 months. Mortality rates in these two patient groups have varied across studies using different interventions, with COPD patients having higher mortality rates than those with HF. Other CR programs in HF have demonstrated reductions in hospitalizations but not mortality rate (Fleg et al., 2015; Jolly et al., 2009). In COPD, patients with moderate/severe disease did not experience improved mortality over 3 years (Guell et al., 2017). However, a meta-analysis suggested that patients with COPD who participated in a pulmonary rehabilitation program after an exacerbation had improved mortality (Puhan, Scharplatz, Troosters, & Steurer, 2005). None of these prior studies included participants with very severe disease, as in the current investigation.

Functional Capacity and Physical Activity

Patients with COPD or HF have impaired skeletal muscle function that decreases functional capacity, resulting in poor physical activity and lower self-reported ratings on the SF-36 physical component scale (Janssen et al., 2011; Jelic & Le Jemtel, 2006). Researchers have frequently identified the 6MWD as a predictor of mortality as well as a prognostic tool in both COPD and HF (Dajczman et al., 2015; O'Connor et al., 2012; Waatevik et al., 2016). Studies have shown the 6MWD to be a better predictor of mortality than FEV_1 (Martinez et al., 2006; Waatevik et al., 2016). It has also been associated with mortality specifically in COPD patients with severe disease (Durheim et al., 2015; Polkey et al., 2013). Dajczman et al. (2015) recently noted that preprogram 6MWD predicted survival at 3 years in severe COPD, where those who were able to walk <150 m had reduced likelihood of survival. These findings are similar to those of Steele et al. (2008), in which improvements in 6MWD, SF36 V physical functioning, and self-efficacy for walking after pulmonary rehabilitation were related to 2-year survival.

Past data have shown that physical activity (total steps/24 hr or self-reported physical function) is associated with mortality in COPD and HF (Blumenthal et al., 2016; Chamberlain et al., 2013; Dwyer et al., 2015). Our results demonstrated that total steps/24 hr and 6MWD were associated with mortality over 60 months. Survivors after 12 months had higher mean total steps/24 hr at baseline than nonsurvivors. Regardless of the disease state, there was an association between higher total steps/24 hr at baseline and reduced risk of mortality in adults (Dwyer et al., 2015).

Symptoms

A high COPD Dyspnea Scale score was a risk factor for mortality at 12 months and 24 months in the entire sample in the

Table 5. Functional Capacity, Symptoms, and Quality of Life at Baseline and 6 and 12 Months After Cardiopulmonary Rehabilitation in Veterans With HF and COPD, Combined, by Mortality Group.

	Time Point			Wald χ^2		*p* Value	
Variable	Baseline (Mean ± *SD*)	6 Months (Mean ± *SD*)	12 Months (Mean ± *SD*)	Group[a]	Group × Time[b]	Group[a]	Group × Time[b]
Functional capacity							
6MWD (m)				2.36	1.13	.12	.29
Total	354.69 ± 117.39	343.17 ± 113.89	314.29 ± 131.29				
Alive at 12 months	367.28 ± 113.48	349.62 ± 131.62	314.29 ± 131.29				
Dead at 12 months	225.70 ± 73.13	192.63 ± 110.74	—				
Total steps/24 hr				1.37	0.89	.24	.34
Total	5,337.27 ± 3,053.33	5,244.92 ± 3,120.10	5,327.00 ± 3,324.02				
Alive at 12 months	5,551.47 ± 3,077.57	5,327.79 ± 3,154.98	5,327.00 ± 3,324.02				
Dead at 12 months	3,141.74 ± 1,699.58	3,558.53 ± 611.42	—				
Symptoms							
COPD Dyspnea Scale				3.99	0.76	.04	.38
Total	3.02 ± 1.40	2.69 ± 1.36	2.85 ± 1.58				
Alive at 12 months	2.90 ± 1.38	2.67 ± 1.32	2.85 ± 1.58				
Dead at 12 months	4.25 ± 0.93	3.17 ± 2.27	—				
Quality of life							
SF-36 V, PCS				0.29	0.54	.59	.46
Total	31.96 ± 8.19	32.83 ± 10.27	32.02 ± 10.99				
Alive at 12 months	32.63 ± 7.95	33.35 ± 10.06	32.02 ± 10.99				
Dead at 12 months	25.12 ± 7.84	19.96 ± 7.56	—				
SF-36 V, MCS				5.92	11.84	.02	.001
Total	48.84 ± 11.81	51.47 ± 11.67	50.04 ± 11.53				
Alive at 12 months	49.11 ± 12.06	51.20 ± 11.81	50.04 ± 11.53				
Dead at 12 months	46.06 ± 9.08	58.05 ± 3.46	—				
SF-36 V, physical function				5.04	1.08	.025	.29
Total	38.63 ± 20.68	43.53 ± 23.55	41.76 ± 25.00				
Alive at 12 months	40.27 ± 20.70	44.67 ± 22.90	41.76 ± 25.00				
Dead at 12 months	21.85 ± 11.31	15.00 ± 25.98	—				
SF-36 V, general health				0.33	2.33	.57	.12
Total	46.69 ± 18.41	48.67 ± 20.88	48.89 ± 20.58				
Alive at 12 months	48.44 ± 17.85	50.16 ± 19.72	48.89 ± 20.58				
Dead at 12 months	28.50 ± 14.82	11.67 ± 16.07	—				
Cardiopulmonary function							
FEV_1				4.65	2.23	.03	.14
Total	39.85 ± 19.20	41.82 ± 22.35	44.62 ± 20.87				
Alive at 12 months	40.83 ± 19.58	42.49 ± 22.49	44.62 ± 20.87				
Dead at 12 months	29.75 ± 11.18	25.50 ± 3.53	—				
NT-proBNP				1.15	2.79	.28	.09
Total	1,086.28 ± 2,013.60	727.10 ± 2,013.60	708.86 ± 1,124.69				
Alive at 12 months	985.93 ± 1,913.75	722.55 ± 968.84	708.86 ± 1,124.69				
Dead at 12 months	2,114.88 ± 2,800.81	863.50 ± 775.70	—				
Self-efficacy							
Self-efficacy exercise				0.30	0.14	.59	.71
Total	6.44 ± 2.33	5.63 ± 2.45	5.28 ± 2.89				
Alive at 12 months	6.61 ± 2.24	5.72 ± 2.42	5.28 ± 2.89				
Dead at 12 months	4.67 ± 2.62	3.22 ± 2.14	—				
Self-efficacy walking				4.02	0.45	.05	.83
Total	2.82 ± 2.42	3.82 ± 3.08	3.20 ± 2.92				
Alive at 12 months	2.96 ± 2.48	3.92 ± 3.09	3.20 ± 2.92				
Dead at 12 months	1.38 ± .92	1.33 ± 1.53	—				

Note. Total $N = 90$; alive at 12 months = 82; dead at 12 months = 8. 6MWD = 6-min walk distance; COPD = chronic obstructive pulmonary disease; HF = heart failure; FEV_1 = forced expiratory volume in 1 s; MCS = mental component score; NT-proBNP = *N*-terminal pro-brain natriuretic peptide; PCS = physical component score; SF-36 V = Short-Form 36–Veterans version.

[a]Group differences between those who were alive at 12 months compared with those who had died by 12 months. [b]Dead and alive Trajectory × Time.

present study, though we found higher mean scores in patients with COPD compared to patients with HF. In general, more patients with COPD experience dyspnea than patients with HF (Janssen et al., 2011; Man et al., 2016). Nearly 60% of patients with COPD complain of moderate or severe shortness of breath related to walking distance (Padeletti et al., 2008; Theander et al., 2014). Shortness of breath is a predictor of both short- and long-term mortality in patients with COPD (Mentz et al., 2012; Yohannes et al., 2016). Depression is another condition prevalent in both COPD and HF (Janssen et al., 2011; Pelle, Gidron, Szabo, & Denollet, 2008). In the present study, we did not find depression to be related to mortality at any time point. Others, however, have found depression to be associated with increased mortality in advanced COPD (Yohannes et al., 2016).

Cardiopulmonary Function

Researchers have commonly used NT-proBNP and BNP levels to predict negative outcomes among patients with HF, to evaluate HF management, and to differentiate COPD from HF in those with shortness of breath (Gaggin & Januzzi, 2013; Jelic & Le Jemtel, 2006; O'Connor et al., 2012; Richter et al., 2013; Troosters et al., 2016). Authors have recommended measurement of NT-proBNP among patients experiencing acute dyspnea, and researchers have used it to predict mortality in patients with acute HF as well as in patients hospitalized with HF (Baggish, van Kimmenade, & Januzzi, 2008; Fonarow, 2012; Richter et al., 2013). In the present analysis, NT-proBNP levels were higher in patients with HF than in those with COPD at every time point. Acute hypoxemia or left ventricular systolic dysfunction in COPD can cause an increase in natriuretic peptide levels, even though the values in COPD are not typically as high as in HF (Rutten et al., 2007). Thus, NT-proBNP may be used to diagnose left ventricular systolic dysfunction in the presence of dyspnea and to predict mortality among patients with both COPD and HF.

Limitations

The parent study was not originally powered to find differences in mortality, so readers are cautioned to interpret statistically significant results conservatively. The sample size in each diagnostic group was small and not normally distributed. A larger proportion of participants had COPD, and most of these had severe disease, with at least 84% classified as GOLD III and IV. Mortality results may be biased because of unbalanced numbers in each diagnostic group. We conducted the study in a male VA population, so generalizability to other groups is limited.

Conclusions

Risk factors for mortality at 12, 24, and 60 months for the entire sample of male veterans with very severe COPD or HF showed that fewer total steps/24 hr, lower 6MWD, and higher NT-proBNP levels were significantly associated with mortality at all time periods in both diagnostic groups. More rigorous selection criteria for CR will result in the participation of fewer patients who are unlikely to receive benefits from the program and who may experience greater discomfort and risk from an exercise-based program. Such patients may attain greater benefit from a less demanding course of more limited exercise, rest, and socialization. More effective selection of CR participants will thus result in more efficient and efficacious use of staff and resources in this highly valued therapeutic field.

Authors' Note

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs.

Author Contributions

Cynthia M. Dougherty contributed to conception, design, acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. Bonnie G. Steele contributed to conception, design, acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. Youjeong Kang contributed to conception, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. Robert L. Burr contributed to conception, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: VA HSR&D, NRI 04-242; NIH, NINR Aging and Informatics Training Program, University of Washington School of Nursing (Kang), T32NR014833.

References

American Heart Association. (2016). *What is heart failure?* Retrieved from http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/About-Heart-Failure_UCM_002044_Article.jsp#.V0VC6fkrJpg

American Lung Association. (2016). *Chronic obstructive pulmonary disease (COPD)*. Retrieved from http://www.lung.org/lung-health-and-diseases/lung-disease-lookup/copd/

Apostolovic, S., Jankovic-Tomasevic, R., Salinger-Martinovic, S., Djordjevic-Radojkovic, D., Stanojevic, D., Pavlovic, M., … Düngen, H. D. (2011). Frequency and significance of unrecognized chronic obstructive pulmonary disease in elderly patients with stable heart failure. *Aging Clinical and Experimental Research*, *23*, 337–342. doi:10.3275/7291

Baggish, A. L., van Kimmenade, R. R., & Januzzi, J. L. Jr. (2008). Amino-terminal pro-B-type natriuretic peptide testing and prognosis in patients with acute dyspnea, including those with acute heart failure. *American Journal of Cardiology*, *101*, 49–55. doi:10.1016/j.amjcard.2007.11.020

Blumenthal, J. A., Smith, P. J., Durheim, M., Mabe, S., Emery, C. F., Martinu, T., … Palmer, S. (2016). Biobehavioral prognostic factors in chronic obstructive pulmonary disease: Results from the INSPIRE-II trial. *Psychosomatic Medicine*, *78*, 153–162. doi:10.1097/PSY.0000000000000260

Boueri, F. M., Bucher-Bartelson, B. L., Glenn, K. A., & Make, B. J. (2001). Quality of life measured with a generic instrument (short form-36) improves following pulmonary rehabilitation in patients with COPD. *Chest*, *119*, 77–84.

Carson, P. E., Anand, I. S., Win, S., Rector, T., Haass, M., Lopez-Sendon, J., … Massie, B. (2015). The hospitalization burden and post-hospitalization mortality risk in heart failure with preserved ejection fraction: Results from the I-PRESERVE trial (Irbesartan in heart failure and preserved ejection fraction). *Journal of the American College of Cardiology. Heart Failure*, *3*, 429–441. doi:10.1016/j.jchf.2014.12.017

Cavanaugh, J. T., Coleman, K. L., Gaines, J. M., Laing, L., & Morey, M. C. (2007). Using step activity monitoring to characterize ambulatory activity in community-dwelling older adults. *Journal of the American Geriatrics Society*, *55*, 120–124.

Cavill, N., Kahlmeier, S., & Racioppi, F. (Eds.). (2006). *Physical activity and health in Europe: Evidence for action*. Copenhagen, Denmark: World Health Organization. Retrieved from http://www.euro.who.int/document/e89490.pdf

Chamberlain, A. M., McNallan, S. M., Dunlay, S. M., Spertus, J. A., Redfield, M. M., Moser, D. K., … Roger, V. L. (2013). Physical health status measures predict all-cause mortality in patients with heart failure. *Circulation: Heart Failure*, *6*, 669–675. doi:10.1161/CIRCHEARTFAILURE.112.000291

Charlson, M., Pompei, P., Ales, K., & MacKenzie, C. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *Journal of Chronic Diseases*, *40*, 373–383.

Dajczman, E., Wardini, R., Kasymjanova, G., Prefontaine, D., Baltzan, M. A., & Wolkove, N. (2015). Six minute walk distance is a predictor of survival in patients with chronic obstructive pulmonary disease undergoing pulmonary rehabilitation. *Canadian Respiratory Journal*, *22*, 225–229.

Duncan, D. (2016). Chronic obstructive pulmonary disease: An overview. *British Journal of Nursing (Mark Allen Publishing)*, *25*, 360–366. doi:10.12968/bjon.2016.25.7.360

Durheim, M. T., Smith, P. J., Babyak, M. A., Mabe, S. K., Martinu, T., Welty-Wolf, K. E., … Blumenthal, J. A. (2015). Six-minute-walk distance and accelerometry predict outcomes in chronic obstructive pulmonary disease independent of global initiative for chronic obstructive lung disease 2011 Group. *Annals of the American Thoracic Society*, *12*, 349–356. doi:10.1513/AnnalsATS.201408-365OC

Dwyer, T., Pezic, A., Sun, C., Cochrane, J., Venn, A., Srikanth, V., … Ponsonby, A. L. (2015). Objectively measured daily steps and subsequent long term all-cause mortality: The tasped prospective cohort study. *PLOS One*, *10*, e0141274. doi:10.1371/journal.pone.0141274

Fleg, J. L., Cooper, L. S., Borlaug, B. A., Haykowsky, M. J., Kraus, W. E., Levine, B. D., … Kitzman, D. W. (2015). Exercise training as therapy for heart failure: Current status and future directions. *Circulation: Heart Failure*, *8*, 209–220. doi:10.1161/CIRCHEARTFAILURE.113.001420

Fonarow, G. C. (2012). Clinical risk prediction tools in patients hospitalized with heart failure. *Reviews in Cardiovascular Medicine*, *13*, e14–e23.

Gaggin, H. K., & Januzzi, J. L. Jr. (2013). Biomarkers and diagnostics in heart failure. *Biochimica et Biophysica Acta*, *1832*, 2442–2450. doi:10.1016/j.bbadis.2012.12.014

Gavazzi, A., De Maria, R., Manzoli, L., Bocconcelli, P., Di Leonardo, A., Frigerio, M., … Deales, A. (2015). Palliative needs for heart failure or chronic obstructive pulmonary disease: Results of a multicenter observational registry. *International Journal of Cardiology*, *184*, 552–558. doi:10.1016/j.ijcard.2015.03.056

Guell, M. R., Cejudo, P., Ortega, F., Puy, M. C., Rodriguez-Trigo, G., Pijoan, J. I., … Galdiz, J. B. (2017). Benefits of long-term pulmonary rehabilitation maintenance program in patients with severe chronic obstructive pulmonary disease. Three-year follow-up. *American Journal of Respiratory and Critical Care Medicine*, *195*, 622–629. doi:10.1164/rccm.201603-0602OC

Haeuber, E., Shaughnessy, M., Forrester, L. W., Coleman, K. L., & Macko, R. F. (2004). Accelerometer monitoring of home-and community-based ambulatory activity after stroke. *Archives of Physical Medicine and Rehabilitation*, *85*, 1997–2001.

Janssen, D. J., Spruit, M. A., Uszko-Lencer, N. H., Schols, J. M., & Wouters, E. F. (2011). Symptoms, comorbidities, and health care in advanced chronic obstructive pulmonary disease or chronic heart failure. *Journal of Palliative Medicine*, *14*, 735–743. doi:10.1089/jpm.2010.0479

Jelic, S., & Le Jemtel, T. H. (2006). Diagnostic usefulness of B-type natriuretic peptide and functional consequences of muscle alterations in COPD and chronic heart failure. *Chest*, *130*, 1220–1230.

Jolly, K., Taylor, R. S., Lip, G. Y., Davies, M., Davis, R., Mant, J., … Stevens, A. (2009). A randomized trial of the addition of home-based exercise to specialist heart failure nurse care: The Birmingham Rehabilitation Uptake Maximisation Study for patients with Congestive Heart Failure (BRUM-CHF) study. *European Journal of Heart Failure*, *11*, 205–213. doi:10.1093/eurjhf/hfn029

Kazis, L. E., Miller, D. R., Clark, J., Skinner, K., Lee, A., Rogers, W., & Linzer, M. (1998). Health-related quality of life in patients served by the department of veterans affairs: Results from the veterans health study. *Archives of Internal Medicine*, *158*, 626–632.

Khazanie, P., Heizer, G. M., Hasselblad, V., Armstrong, P. W., Califf, R. M., Ezekowitz, J., … Starling, R. (2015). Predictors of clinical outcomes in acute decompensated heart failure: Acute study of clinical effectiveness of nesiritide in decompensated heart failure outcome models. *American Heart Journal*, *170*, 290–297. doi:10.1016/j.ahj.2015.04.006

Li, L. S., Caughey, G., & Johnston, K. (2014). Comorbidity associated with referral to pulmonary rehabilitation in people hospitalized with chronic obstructive pulmonary disease. *Journal of*

Cardiopulmonary Rehabilitation and Prevention, *34*, 430–436. doi:10.1097/HCR

Louvaris, Z., & Vogiatzis, I. (2015). Physiological basis of cardiopulmonary rehabilitation in patients with lung or heart disease. *Breathe (Sheffield, England)*, *11*, 120–127. doi:10.1183/20734735.021114

Man, W. D., Chowdhury, F., Taylor, R. S., Evans, R. A., Doherty, P., Singh, S. J., … Cowie, M. R. (2016). Building consensus for provision of breathlessness rehabilitation for patients with chronic obstructive pulmonary disease and chronic heart failure. *Chronic Respiratory Disease*, *13*, 229–239. doi:10.1177/1479972316642363

Martinez, F. J., Foster, G., Curtis, J. L., Criner, G., Weinmann, G., Fishman, A., … Wise, R. (2006). Predictors of mortality in patients with emphysema and severe airflow obstruction. *American Journal of Respiratory and Critical Care Medicine*, *173*, 1326–1334. doi:10.1164/rccm.200510-1677OC

McCarthy, B., Casey, D., Devane, D., Murphy, K., Murphy, E., & Lacasse, Y. (2015). Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*, *23*, CD003793. doi:10.1002/14651858.CD003793.pub3

Mentz, R. J., Schmidt, P. H., Kwasny, M. J., Ambrosy, A. P., O'Connor, C. M., Konstam, M. A., … Gheorghiade, M. (2012). The impact of chronic obstructive pulmonary disease in patients hospitalized for worsening heart failure with reduced ejection fraction: An analysis of the EVEREST trial. *Journal of Cardiac Failure*, *18*, 515–523. doi:10.1016/j.cardfail.2012.04.010

Miller, M., Crapo, R., Hankinson, J., Brusasco, V., Burgos, F., Casaburi, R., … Wanger, J. (2005). General considerations for lung function testing. *European Respiratory Journal*, *26*, 153–161.

Nguyen, H. Q., Burr, R. L., Gill, D. P., & Coleman, K. (2011). Validation of the step watch device for measurement of free-living ambulatory activity in patients with chronic obstructive pulmonary disease. *Journal of Nursing Measurement*, *19*, 76–90.

Nunez, J., Nunez, E., Bayes-Genis, A., Fonarow, G. C., Minana, G., Bodi, V., … Sanchis, J. (2016). Long-term serial kinetics of N-terminal pro B-type natriuretic peptide and carbohydrate antigen 125 for mortality risk prediction following acute heart failure. *European Heart Journal. Acute Cardiovascular Care*, *6*, 685–696. doi:10.1177/2048872616649757

O'Connor, C. M., Whellan, D. J., Wojdyla, D., Leifer, E., Clare, R. M., Ellis, S. J., … Lee, K. L. (2012). Factors related to morbidity and mortality in patients with chronic heart failure with systolic dysfunction: The HF-ACTION predictive risk score model. *Circulation: Heart Failure*, *5*, 63–71. doi:10.1161/CIRCHEARTFAILURE.111.963462

Osthoff, M., Jenkins, C., & Leuppi, J. (2013). Chronic obstructive pulmonary disease—A treatable disease. *Swiss Medical Weekly*, *143*, w13777. doi:10.4414/smw.2013.13777

Padeletti, M., Relic, S., & LeJemtel, T. H. (2008). Coexistent chronic obstructive pulmonary disease and heart failure in the elderly. *International Journal of Cardiology*, *125*, 209–215. doi:10.1016/j.ijcard.2007.12.001

Pelle, A. J., Gidron, Y. Y., Szabo, B. M., & Denollet, J. (2008). Psychological predictors of prognosis in chronic heart failure. *Journal of Cardiac Failure*, *14*, 341–350. doi:10.1016/j.cardfail.2008.01.004

Polkey, M. I., Spruit, M. A., Edwards, L. D., Watkins, M. L., Pinto-Plata, V., & Vestbo, J., … Coxson, H. O. (2013). Six-minute-walk test in chronic obstructive pulmonary disease: Minimal clinically important difference for death or hospitalization. *American Journal of Respiratory and Critical Care Medicine*, *187*, 382–386. doi:10.1164/rccm.201209-1596OC

Puhan, M. A., Scharplatz, M., Troosters, T., & Steurer, J. (2005). Respiratory rehabilitation after acute exacerbation of COPD may reduce risk for readmission and mortality—A systematic review. *Respiratory Research*, *6*, 54.

Richter, B., Koller, L., Hohensinner, P. J., Zorn, G., Brekalo, M., Berger, R., … Niessner, A. (2013). A multi-biomarker risk score improves prediction of long-term mortality in patients with advanced heart failure. *International Journal of Cardiology*, *168*, 1251–1257. doi:10.1016/j.ijcard.2012.11.052

Rutten, F. H., Cramer, M. J., Zuithoff, N. P., Lammers, J. W., Verweij, W., Grobbee, D. E., & Hoes, A. W. (2007). Comparison of B-type natriuretic peptide assays for identifying heart failure in stable elderly patients with a clinical diagnosis of chronic obstructive pulmonary disease. *European Journal of Heart Failure*, *9*, 651–659.

Sagar, V. A., Davies, E. J., Briscoe, S., Coats, A. J., Dalal, H. M., Lough, F., … Taylor, R. S. (2015). Exercise-based rehabilitation for heart failure: Systematic review and meta-analysis. *Open Heart*, *2*, e000163. doi:10.1136/openhrt-2014-000163

Singh, J. A., & Yu, S. (2016). Utilization due to chronic obstructive pulmonary disease and its predictors: A study using the U.S. National Emergency Department Sample (NEDS). *Respiratory Research*, *17*, 1. doi:10.1186/s12931-015-0319-y

Sprenkle, M. D., Niewoehner, D. E., Nelson, D. B., & Nichol, K. L. (2004). The veterans short form 36 questionnaire is predictive of mortality and health-care utilization in a population of veterans with a self-reported diagnosis of asthma or COPD. *Chest*, *126*, 81–89. doi:10.1378/chest.126.1.81

Steele, B. G., Belza, B., Cain, K. C., Coppersmith, J., Lakshminarayan, S., Howard, J., & Haselkorn, J. K. (2008). A randomized clinical trial of an activity and exercise adherence intervention in chronic pulmonary disease. *Archives of Physical Medicine and Rehabilitation*, *89*, 404–412. doi:10.1016/j.apmr.2007.11.003

Steele, B. G., Dougherty, C. M., Burr, R. L., Gylys-Colwell, I., & Hunziker, J. (2017). A feasibility trial of two rehabilitation models in severe cardiopulmonary illness. *Rehabilitation Nursing*. Advance online publication. doi:10.1097/rnj.0000000000000115

Theander, K., Hasselgren, M., Luhr, K., Eckerblad, J., Unosson, M., & Karlsson, I. (2014). Symptoms and impact of symptoms on function and health in patients with chronic obstructive pulmonary disease and chronic heart failure in primary health care. *International Journal of Chronic Obstructive Pulmonary Disease*, *9*, 785–794. doi:10.2147/COPD.S62563

Troosters, T., Bourbeau, J., Maltais, F., Leidy, N., Erzen, D., De Sousa, D., … Hamilton, A. (2016). Enhancing exercise tolerance and physical activity in COPD with combined pharmacological and non-pharmacological interventions: PHYSACTO randomised,

placebo-controlled study design. *BMJ Open*, *6*, e010106. doi:10.1136/bmjopen-2015-010106

Troosters, T., & VanRemoortel, H. (2009). Pulmonary rehabilitation and cardiovascular disease. *Seminars in Respiratory and Critical Care Medicine*, *30*, 675–683.

Tzanis, G., Philippou, A., Karatzanos, E., Dimopoulos, S., Kaldara, E., Nana, E., … Nanas, S. (2016). Effects of high-intensity interval exercise training on skeletal myopathy of chronic heart failure. *Journal of Cardiac Failure*, *23*, 36–46. doi:10.1016/j.cardfail.2016.06.007

van der Molen, T., Willemse, B. W., Schokker, S., ten Hacken, N. H., Postma, D. S., & Juniper, E. F. (2003). Development, validity and responsiveness of the clinical COPD questionnaire. *Health and Quality of Life Outcomes*, *1*, 13.

Waatevik, M., Johannessen, A., Gomez Real, F., Aanerud, M., Hardie, J. A., Bakke, P. S., & Lind Eagan, T. M. (2016). Oxygen desaturation in 6-min walk test is a risk factor for adverse outcomes in COPD. *European Respiratory Journal*, *48*, 82–91. doi:10.1183/13993003.00975-2015

Waschki, B., Kirsten, A. M., Holz, O., Mueller, K. C., Schaper, M., Sack, A. L., … Watz, H. (2015). Disease progression and changes in physical activity in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine*, *192*, 295–306. doi:10.1164/rccm.201501-0081OC

Watson, L. C., & Pignone, M. P. (2003). Screening accuracy for late-life depression in primary care: A systematic review. *Journal of Family Practice*, *52*, 956–964.

Yohannes, A. M., Raue, P. J., Kanellopoulos, D., McGovern, A., Sirey, J. A., Kiosses, D. N., … Alexopoulos, G. S. (2016). Predictors of all-cause mortality in patients with severe COPD and major depression admitted to a rehabilitation hospital. *Chest*, *149*, 467–473.