Spirometry, the St. George's Respiratory Questionnaire, and other clinical measures as predictors of medical costs and COPD exacerbation events in a prospective cohort

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ABSTRACT

Propose: *We conducted a prospective clinical cohort study of 300 established COPD patients randomly recruited from one managed care system to examine how well a battery of spirometry, exercise, and health status measures, including the St. Georges Respiratory Questionnaire (SGRQ), collected at baseline correlated with future healthcare costs and COPD exacerbations, and which were the most robust predictors of these outcomes in multivariate analyses.*

Methods: *All COPD patients treated over a 24-month period in the managed care system who met the utilization-based inclusion criteria were randomly recruited until 300 patients completed all clinical testing. Their healthcare utilization over the next 24 months was captured from administrative databases and used to develop multivariate models for healthcare costs and COPD exacerbations.*

Results: *The mean age of participants was 71 years, 62% were male, mean percent predicted FEV_1 (%$pFEV_1$) was 60%, and median total healthcare costs in the follow-up period were $900 per month. Many factors correlated with increased total costs, but in linear regression models the parameters most predictive were age, Charlson comorbidity score, spirometry measures (%$pFEV_1$ or other measures, depending on the model), and the SGRQ Activity score. These same measures were also the most predictive of future exacerbations. Other measures such as the Borg score and treadmill time were significant in some models.*

Conclusions: *Four clinical measures (age, comorbidities, spirometry, and the SGRQ Activity score) are independent predictors of future healthcare costs and COPD exacerbations. Multidimensional scales for measuring COPD severity that are in development will need to account for these measures.*

Key words: Chronic obstructive pulmonary disease, costs, exacerbations, St George's Respiratory Questionnaire

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INTRODUCTION

Chronic obstructive pulmonary disease is the variable combination of chronic bronchitis and em-

physema, which share a common cause (cigarette smoking) and physiologic outcome (expiratory airflow obstruction). Traditionally, the severity of COPD has been graded by the degree of airflow obstruction, as described by the percent of predicted FEV_1 (%$pFEV_1$). Longitudinal studies of smokers dating back to the original Fletcher and Peto London cohorts have confirmed the validity of using post-bronchodilator %$pFEV_1$ as a measure of COPD severity and disease progression. However, physicians who treat COPD patients regularly note that %$pFEV_1$ does not reliably correlate with an individual patient's clinical status. It is not unusual to find patients with severe airflow obstruction who lead normal active lifestyles, while some with moderate obstruction are functionally disabled by their respiratory disease.

The GOLD consensus report was revised in 2011 to address the limitations of relying solely on spirometry to characterize the severity and progression of COPD, adding an evaluation of chronic respiratory symptoms and the history of exacerbations.[1] Two well validated respiratory symptom questionnaires, the modified Medical Research Council (mMRC) and the COPD Assessment Test (CAT), were specifically recommended. Using these in addition to GOLD spirometric classifications, individuals are assessed as low risk (groups A [less symptoms] and B [more symptoms]) or high risk (C [less symptoms] and D [more symptoms]). However, the best metrics, other than spirometry, for objectively assessing COPD severity are still uncertain. Limitations in the new GOLD COPD classification system have been noted. In particular, the mMRC and CAT have markedly different results when applied to well characterized COPD populations, and the ABCD severity levels do not correlate well with risk for future exacerbations and other clinical outcomes.[2-4] There is a need to better describe COPD severity in ways that are relevant to patients, providers, and those interested in measuring the benefits of COPD treatment. To accomplish this we need a better understanding of the clinical measures that have the best ability to predict clinically important outcomes such as healthcare costs and COPD exacerbation risk among patients treated in the general population.

The goal of this project was to prospectively examine how spirometry and a multidimensional COPD symptom and impact questionnaire (the St. Georges Respiratory Disease Questionnaire [SGRQ]), plus a panel of other common respiratory and health status measures, compare in their ability to predict exacerbation rates and healthcare costs. To accomplish this, we conducted a prospective study of 300 established patients randomly recruited from one managed care system and examined how well the battery of spirometry, exercise, and health status measures collected at baseline correlated with future healthcare costs and COPD exacerbations and which were robust predictors of these outcomes in multivariate analyses.

Methods

The COPD patients recruited for this study were enrolled in a large regional managed care provider serving the Southwestern United States. Patients were required to have one hospitalization or two outpatient visits associated with COPD (ICD-9 diagnosis codes 491.x, 492.x, or 496) in the 12 months prior to recruitment, be at least age 40 but less than age 90 on the date of the qualifying COPD claim, and be continuously enrolled with the managed care provider for at least 24 months prior to testing. They also had to be able to safely walk on a treadmill at a speed of 2 miles per hour for at least 30 seconds, be able to read the informed consent form and study questionnaires in English, and be capable of completing all tests and questionnaires in one day. Based on inclusion criteria, a randomized list of 522 potential study candidates was constructed. Patients were sequentially contacted until 300 participants were recruited and enrolled. The study protocol was approved and supervised by the Lovelace Institutional Review Board in Albuquerque, NM.

Patient Assessment

All participants were required to complete the following series of lung function tests, exercise tests, health status measures, and symptom questionnaires.

A. Spirometry and Exercise Testing

Spirometry was performed using equipment and procedures recommended by the American Tho-

racic Society by a licensed respiratory therapist certified in pulmonary function testing. Key measurements included:

- Spirometry pre and post four 90 mcg doses of albuterol delivered using a spacer device.
- A slow vital capacity maneuver.
- An exercise tolerance test wherein test subjects walked on a treadmill set at 2 miles per hour with no slope until they were too tired to continue or they reached 12 minutes.
- Oxygen saturation at rest just prior to exercise testing.
- Lowest oxygen saturation achieved during exercise testing.
- The Borg Dyspnea Scale before and immediately after exercise testing (scores range from 0 [no difficulty breathing] to 10 [maximal difficulty]).

B. Health Status Measures

The SGRQ is a respiratory disease-specific instrument composed of 72 items within three domains: symptoms, activity, and impact, which are scored individually. The composite score, ranging from 0 (best respiratory health) to 100 (worst respiratory health) is often reported in clinical trials, but because we had interest in the performance of the subscales, we examined them individually.

Comorbidity, Medical Cost, and COPD Exacerbation Data

The Deyo adaptation of the Charlson Index was used to identify and score potentially significant comorbidities.[5] While the original Charlson Index was developed using hospitalization records, for this project we identified comorbidities from both inpatient and outpatient billing records for the two years prior to testing.

Utilization data for all study participants were collected for up to the earliest of 24 months post-testing, the date of death, or disenrollment date. Costs were calculated using Medicare rates for specific procedures whenever available. For procedure codes not covered by Medicare, the billed amount was used. Outpatient pharmacy costs were estimated using the average wholesale prescription. Cost data were standardized and reported in 2013 US dollars using the Medical Care Consumer Price Index.

Classification of Exacerbation Severity

- Moderate Exacerbation: An outpatient visit with a respiratory diagnosis plus a prescription claim for an antibiotic or oral corticosteroid within two days of the visit.
- Emergency Department (ED) Exacerbation: An ED visit with a COPD principal (or first listed) diagnosis with the patient discharged to home.
- Severe Exacerbation: A hospital admission with a COPD principal discharge diagnosis.

Analyses

Patient costs – inpatient, outpatient, outpatient pharmacy, and total costs – were aggregated by month and were modeled as a continuous response variable using a generalized linear regression procedure. PROC MIXED in SAS was utilized in order to adjust for the repeated observations for each study subject over time. The degree of correlation between monthly costs at the patient level was assessed by the intraclass correlation coefficient (ICC). Costs were transformed to a log scale. Incident rate ratios (IRR) were estimated for exacerbations using logistic regression models for the events (Poisson distribution). The number of months of follow-up was variable; therefore, the models incorporated an offset for the number of months each study subject was followed.

To select the strongest measures within each domain (demographic, physiologic, and quality of life), we conducted separate regression analyses investigating the relationship between each baseline measure and major cost outcomes (inpatient, outpatient, pharmacy, and total costs) and exacerbations, adjusted for patient age and sex. An adjustment was not made for multiple statistical tests. Baseline measures within each domain were chosen that had the strongest relationship as determined by a high F-statistic for cost outcomes and a high Wald chi-square statistic for admissions and exacerbations.

Results

Demographic and clinical characteristics of study participants are presented in Table 1. Overall, study subjects were a representative sample of the larger COPD population eligible for this study. The mean age at testing was 70.9 years (interquartile range (IQR): 63-74), similar to the mean age of the total eligible COPD population (69.1 years; IQR: 62-74). One important difference is that women comprised 53% of the COPD patients eligible for this study, but only 38% of the study subjects. Overall, the mean baseline %pFEV1 was 60.2% (IQR: 40-80%), similar to a larger cohort of COPD patients from this health plan who were randomly selected for medical record and pulmonary function test abstraction (59.4%; IQR: 38-80%).[6] The mean Charlson Index (1.08) was also similar to that for the abstracted cohort (1.10).

There were a few significant baseline clinical differences by sex (Table 1). Men had a higher Charlson Index score (P<0.01) and average cigarette pack-year smoking history (P<0.001), but women were more likely to still be smoking at the assessment or be never-smokers (P<0.01). However, proportions of men and women reporting wheezing in the previous year, proportions having airflow obstruction substantially reduced by albuterol, baseline spirometry results, treadmill test results, and SQRQ scores were remarkably similar between the sexes.

The mean monthly direct medical costs, exacerbation events, and deaths during the 24 month follow-up period are provided in Table 2. There were no significant differences in these outcomes by sex.

For most patients pharmacy costs are fairly uniform from month to month, and this was demonstrated by the high correlation (0.55) in monthly costs for patients for pharmacy costs. Inpatient costs, on the other hand, had a low correlation (0.09) from month to month for patients as these costs are not regularly incurred by patients. Total costs were significantly correlated with the total number of chronic illnesses, the Charlson Index, wheezing in the last 12 months, the %p FVC or %p FEV1 (pre- or post-bronchodilator), treadmill time, the Borg score (pre- and post-treadmill), lowest oxygen saturation with exercise, and all SGRQ subscales. Smoking and asthma history, the resting Borg score, and baseline oxygen saturation were not predictors of increased total costs. Only the Charlson Index, the spirometry measures, treadmill time, and the SGRQ impact and activity subscales were significant predictors in all three of the subdivisions of total costs (inpatient, outpatient, or outpatient pharmacy costs).

The clinical factors that continued to be independently predictive of increased future cost after adjustment for other variables are presented in Table 3. Age was included as a covariate in all models even though it was not a significant contributor to the inpatient or pharmacy cost models. Only those with the strongest association with increased future cost within each domain group (e.g., spirometry, SGRQ) were included in the final models.

As a sensitivity analysis, subjects who died during the follow-up period (n=22) were excluded. None of the parameter estimates or their significance was substantially affected by excluding these subjects, indicating that these parameters are relevant predictors of cost whether or not a patient survives the next 24 months (data not shown).

In general, the factors that were significantly correlated with increased future medical costs on a univariate basis were also associated with increased future risk of exacerbations, with the exception of the number of chronic illnesses or the Charlson Index. As in the cost models, only those factors with the strongest association with future exacerbations within each group were included in the final models (Table 4). Age and sex were kept as parameters in all models, although neither were significant contributors to the ED Exacerbation model. In general, the domains independently associated with increased risk of exacerbations (Charlson Index, post-albuterol %pFEV1 [less than mean], pre-albuterol FVC [less than mean], and SGRQ activity score [greater than mean]) were also associated with increased costs, with the additional finding that treadmill time [greater than mean] was an independent predictor for severe COPD exacerbations.

Table 1 Baseline demographic and clinical characteristics (N (%) or mean [SD])

	Men (N = 185)	Women (N = 115)	P-value
	N (%) or mean [SD]		
Age (years)	71.6 [10.1]	69.8 [10.4]	
Hispanic ethnicity	27 (14.6%)	14 (12.2%)	
Total chronic illnesses other than COPD[a]	2.0 [1.5]	2.1 [1.4]	
Charlson Index[a]	1.2 [1.1]	0.9 [0.8]	**
Smoking history			
Pack-years	57.2 [34.8]	44.5 [24.6]	***
Smoking status			**
Current	37 (20.0%)	35 (30.4%)	
Former	135 (73.0%)	62 (53.9%)	
Never smoked	13 (7.0%)	18 (15.7%)	
Diagnosis[a] or history of asthma	71 (38.4%)	54 (47.0%)	
Experienced wheezing in previous 12 months	123 (66.5%)	79 (68.7%)	
Improvement in FEV1 > 12% or 200cc after albuterol	52 (28.1%)	33 (28.7%)	
Percent Predicted Spirometry Values			
Pre-albuterol %pFEV$_1$	59.8 [26.5]	60.7 [23.4]	
Post-albuterol %pFEV$_1$	63.4 [26.7]	65.4 [23.7]	
Pre-albuterol %pFVC	89.9 [25.2]	83.2 [20.5]	*
Post-albuterol %pFVC	94.3 [23.9]	87.9 [19.1]	*
Treadmill exercise			
Treadmill time (min)	7.3 [4.2]	7.4 [4.4]	
Borg score, baseline	1.5 [1.6]	1.7 [1.7]	
Borg score, post-treadmill	3.8 [1.6]	3.7 [1.5]	
Oxygen			
Resting O_2 saturation (%)	91.6 [12.0]	91.7 [12.7]	
Lowest exercise O_2 saturation (%)	88.5 [5.7]	89.1 [5.4]	
SGRQ Scales			
Symptoms score	49.8 [24.6]	50.0 [23.9]	
Impact score	30.5 [17.8]	33.6 [20.1]	
Activity score	59.0 [26.1]	63.3 [24.0]	

* P<0.05, ** P<0.01, *** P<0.001

[a] Calculated using utilization data from the 12-months prior to the baseline visit

Abbreviations: cc, cubic centimeters; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; N, number of subjects; O_2, oxygen; SD, standard deviation; SGRQ, Saint George's Respiratory Questionnaire

Table 2 Monthly health care costs, exacerbation rates, and deaths in the 2-year follow-up period

	Men (N= 185)	Women (N = 115)
Monthly costs [a]	*Mean (median)* [IQR]	
Inpatient	*$854 (0)* [0, $531]	*$546 (0)* [0, $425]
Outpatient	*$993 ($703)* [$405, $1083]	*$806 ($646)* [$336, $1059]
Pharmacy	*$148 ($111)* [$40, $206]	*$150 ($131)* [$51, $221]
Total direct cost	*$1995 ($924)* [$355, $1924]	*$1502 ($875)* [$326, $1746]
COPD exacerbations [b]	*Mean* N (% with 1 or more)	
Moderate	*0.65* 85 (46.0%)	*0.72* 62 (53.9%)
Emergency department	*0.16* 29 (15.7%)	*0.14* 16 (13.9%)
Severe	*0.18* 34 (18.4%)	*0.16* 13 (11.3%)
Deaths within 24 months after testing	N (%)	
	15 (8.1%)	7 (6.1%)

[a] Cost are expressed as US dollars adjusted for inflation to 2013.

[b] Exacerbation rates expressed as the mean events per patient per year.

ED, emergency department; IQR, Interquartile range (25th and 75th percentile values)

No significant difference between male/female (Wilcoxon nonparametric test)

Table 3 Final generalized linear regression models for future inpatient, outpatient, pharmacy, and total medical costs with coefficients for the significant baseline clinical measures.

Baseline Characteristic	Reference	Parameter Coefficient Estimate (p-value)			
		Inpatient Costs[a]	Outpatient Costs[a]	Pharmacy Costs[a]	Total Costs[a]
Age > 75	Age ≤ 75		0.506 (0.009)		0.463 (0.02)
Charlson Index = 1	Charlson Index = 0	0.172 (0.02)	1.168 (<.001)	0.821 (0.005)	1.227 (<.001)
Charlson Index > 1		0.242 (0.006)	1.691 (<.001)	0.977 (<.001)	1.636 (<.001)
Pre-albuterol %pFEV1	continuous [b]		-0.009 (0.03)		
Post-albuterol %pFVC	continuous [b]	-0.004 (0.01)		-0.012 (0.008)	-0.016 (0.002)
Borg, post-treadmill	continuous [b]		0.175 (0.01)		
SGRQ Activity	continuous [b]		0.012 (0.007)	0.011 (0.02)	0.012 (0.007)
ICC for repeated observations per patient		0.09	0.36	0.55	0.42

[a] Costs were transformed to a log scale, [b] Continuous variables were normalized around their mean, and rounded to the nearest integer; parameter estimate is for impact of one integer unit from mean.

Abbreviations: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; ICC, intraclass correlation coefficient; SGRQ, Saint George's Respiratory Questionnaire

Discussion

Among the range of demographic characteristics, physiologic tests, symptom assessments, and health status questionnaires that we examined in this prospective cohort study, four measures (age, Charlson Index, spirometry, and SGRQ scores) were the most consistent predictors of both healthcare costs and future exacerbations. Older age was strongly associated with higher outpatient costs and total costs as well as severe exacerbations. A higher Charlson comorbidity score was a very strong factor for higher costs across all categories and for ED and severe exacerbations. Less severe airflow obstruction as indicated by spirometry was associated with reduced costs and reduced exacerbations. Higher BORG post-treadmill scores, indicating greater difficulty breathing, were associated with greater outpatient costs, and longer treadmill time, indicating better exercise capacity, with reduced risk of severe exacerbation. Higher SGRQ Activity scores were associated with higher outpatient, outpatient pharmacy, and total costs as well as increased risk of moderate and severe exacerbations.

These findings demonstrate that COPD severity assessment systems are likely to be unstable unless they also account for the confounding influences of comorbidity and advanced age. Other COPD multi-dimensional assessments have also combined physiologic measures and symptoms scores, most famously the BODE system which combined measures of body mass, airflow obstruction, dyspnea, and exercise into a composite score that was a better predictor of outcomes than spirometry alone.[7] We recently demonstrated that a 'quasi-BODE' system relying on

Table 4 Incident rate ratio multivariate models of COPD exacerbations

		Moderate		Emergency Department		Severe	
Variable	**Reference**	**IRR**	**P-value**	**IRR**	**P-value**	**IRR**	**P-value**
Age 65-75	Age < 65	0.75	0.04				
Age > 75		0.79	0.09			1.62	0.04
Charlson Index = 1	Charlson Index = 0	1.77	0.001	3.07	0.01	6.34	0.01
Charlson Index > 1		1.95	<.001	3.88	0.004	4.64	0.04
Post-albuterol %pFEV1	continuous [a]	0.99	<.001			0.98	0.002
Pre-albuterol %pFVC	continuous [a]			0.98	<.001		
Treadmill time	continuous [a]					0.89	<.001
SGRQ Activity	continuous [a]	1.01	<.001			1.02	0.003

IRR values <1.0 indicate a reduced risk of exacerbation occurrence. IRR values >1.0 indicate an increased risk of exacerbation occurrence.

[a] Continuous variables were normalized around their mean, and rounded to the nearest percentage point; parameter estimate is for impact of one integer unit from mean (i.e., a post-albuterol %pFEV1 score 10 points higher than the mean of 60% would indicate a reduced risk of severe exacerbation indicated by an IRR of 0.82 (calculated as 0.98^{10}).

FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; IRR, incidence rate ratio; SGRQ, Saint George's Respiratory Questionnaire

peak expiratory flow rate and other measures that are easier to obtain than those of the original BODE worked as well or better when predicting survival and other outcomes among COPD patients.[8]

While a multidimensional assessment is clearly a better strategy for assessing patients, there is still great uncertainty about exactly which symptom questions are the most efficient for describing current respiratory health status and the best predictors of future outcomes. It is highly likely that age and comorbidities affect perceptions of symptoms and clinical outcomes; for example, congestive heart failure causes dyspnea indistinguishable from that caused by COPD, and the combination of heart failure and COPD has very serious prognostic implications. If a COPD severity assessment system does not account for the impact of age and comorbidities, then it is likely to suffer from the limitations that we observe in even the best systems that have been developed to date.

The SGRQ, first published in 1991, has been well validated in prospective clinical trials, longitudinal cohort studies, and numerous cross-sectional analyses of COPD patients.[9,10] However, its 76 questions and complicated scoring system make it unwieldy for clinical use. We chose to analyze the three subscales and found that the activity score was the most useful. This

suggests that as we try to develop a clinically practical but statistically robust clinical assessment tool, activity measures are likely to be the most efficient. This is consistent with the experience with the mMRC dyspnea scale questionnaire, wherein patients are simply asked one item about how shortness of breath limits their ability to conduct activities of daily living.

There are limitations of this study that should be acknowledged when considering the results. First, women were less likely to volunteer to participate in our study; though 53% of COPD patients treated in this system were women, only 36% of study subjects were women; however we did adjust for sex and age in our analyses. Our study was conducted in a regional healthcare system of the US. Other systems, based on their clinical practices or population differences, may have different factors that affect COPD outcomes. Finally, even though there were no specific interventions included in this study, it is possible that participation in it may have altered the patients' behavior in ways that affected their outcomes.

In summary, we found that four measures (age, comorbidities, spirometry, and the SGRQ Activity score) are independent predictors of future healthcare costs and COPD exacerbations. These were validated using 'real-life' data from COPD patients treated in the general population, a population likely to be more generalizable than data collected from highly selected clinical trials populations. As we search for better ways to develop valid COPD severity scoring systems, it will be important to account for the effects and interactions among these four measures.

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