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Functional Capacity, Health Status, and Inflammatory Biomarker Profile in a Cohort of Patients With Chronic Obstructive Pulmonary Disease

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■ **PURPOSE:** Prior research has shown a significant relationship between 6-minute walking distance (6MWD) and health-related quality of life (HRQOL) in patients with chronic obstructive pulmonary disease (COPD). However, few studies have examined this relationship above and below the 350-m threshold that prognosticates survival and whether serum biomarkers could provide insight into the causes of quality-of-life differences above and below this threshold.

■ **METHODS:** Measures of lung function, 6MWD, and HRQOL were compared in patients with COPD. Differences in HRQOL domains and serum biomarkers were compared in patients whose 6MWD were > or < 350 m.

■ **RESULTS:** In patients walking < 350 m, scores in the physical domains of the SF-36 and the St. George's Respiratory Questionnaire (SGRQ) were significantly different from scores of their counterparts with greater 6MWD. However, there was no association between any biomarkers and the physical domains of the SF-36 and the SGRQ. In patients walking < 350 m, only the IL-8 levels were associated with lower scores in SF-36 domains of emotional role, pain, vitality, and mental health (average r = −0.702; P = .01). In contrast, in patients walking > 350 m, surfactant protein D levels were associated with higher SF-36 scores in general pain, vitality, and social functioning (average r = 0.42; P = .04).

■ **CONCLUSIONS:** In COPD, there is an association between 6MWD and the physical domains of the SF-36 and SGRQ in those patients walking < 350 m. The physical differences between patients walking < or > 350 m are not related to systemic inflammation. The association between interleukin 8 with nonphysical domains in patients with 6MWD < 350 m suggests that inflammation may play a larger role in the perceptive domain than previously recognized.

K E Y W O R D S

biomarkers

chronic obstructive pulmonary disease

health-related quality of life

pulmonary rehabilitation

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Chronic obstructive pulmonary disease (COPD) is a leading cause of mortality and disability in the world.[1] Impaired functional capacity is common in COPD and likely multifactorial, including severe airflow limitation,[2] muscle wasting[3] and depression,[4] among other systemic manifestations of the disease. Systemic inflammation has been implicated in the development of these extrapulmonary manifestations of COPD.[5,6] Therefore, serum biomarkers of local and systemic inflammation have gained increasing attention as associations to meaningful clinical outcomes, such as mortality and hospitalizations, have been established.[7] Studies thus far, however, have not examined the relationship between these serum biomarkers and health-related quality-of-life (HRQOL) domains in COPD patients with severe functional limitations.

In COPD, forced expiratory volume in 1 second (FEV_1) has been historically used to predict functional outcomes and even mortality, despite its weak relationship to both of these important outcomes. More recently, exercise capacity has emerged as one of the most important prognostic indicators in COPD. Although maximal oxygen uptake ($\dot{V}O_2max$) obtained from cardiopulmonary exercise testing has been shown to be a predictor of mortality in COPD, such testing is not always readily available or cost-effective.[8] The 6-minute walking distance (6MWD), on the contrary, is a quick reproducible exercise field test that predicts mortality in patients with COPD.[9,10] Although the average 6MWD is low in severe COPD, the distribution is wide within all severity categories of COPD.[11] In studies where both 6MWD and FEV_1 have been compared, the 6MWD was a better predictor of mortality than the FEV_1[9] and evidence suggests that a value of 350 m is the threshold below which patients experience a linear increased risk of hospitalization and mortality.[12,13]

Relationships between 6MWD as a continuous physiologic measure and HRQOL measures have been established in COPD. The 6MWD has been shown to correlate with both disease-specific and generic HRQOL instruments, such as the St. George's Respiratory Questionnaire (SGRQ)[14] and the Medical Outcomes SF-36 questionnaire (SF-36),[15] respectively. Although the disease-specific SGRQ has been validated in large therapeutic trials, such as TORCH and UPLIFT,[16] and in observational studies such as ECLIPSE,[2] relatively few studies have examined the relationship of the 6MWD with generic measures of quality of life such as the SF-36, which measures overall health status including effects of comorbid diseases. Of importance, no study has evaluated the relationship between HRQOL domains of the SGRQ and SF-36 and patients' ability to walk greater or less than 350 m,[17] despite the considerable prognostic value of this functional threshold.

The HRQOL measures have been shown to be robust predictors of 6MWD[2] and mortality[18] in COPD. Thus, understanding the HRQOL profile of COPD patients with poor functional status is essential to our clinical understanding of the true burden of illness engendered by COPD in this functionally limited population. In addition, understanding possible biologic causes of the HRQOL profile of those with 6MWD $<$ 350 m may provide insight into how best to stratify and manage these patients.

Therefore, the purpose of this study was 2-fold. First, this study sought to establish which domains of HRQOL are related to poor functional capacity as measured by the 6MWD $<$ 350 m in COPD. Subsequently, this study examined the link between inflammatory biomarkers and these domains of HRQOL in patients with 6MWD above and below the 350-m threshold. We hypothesized that HRQOL domain scores and the relationships between HRQOL domains and biomarker profiles would differ above and below the 350-m threshold that confers survival prognosis and is currently proposed as a stratification tool by the COPD Foundation Biomarker Qualification Consortium.[12,13,19]

SUBJECTS AND METHODS

Study Population

Subjects were participants in the observational study RES19044 ("A Multi-center Cohort Study to Evaluate Radiological, Physiological and Biochemical Biomarkers in Patients With Chronic Obstructive Pulmonary Disease and Age and Gender Matched Controls") enrolled in 2004 and followed until 2008. RES19044 was approved by the institutional review boards of St. Elizabeth's Medical Center (Protocol #00195) and the University of Pennsylvania (Protocol #801096). Subjects were diagnosed on the basis of the 2007 Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria of airflow obstruction[20] and assigned to 1 of 5 groups: healthy nonsmokers; current or former smokers without airflow obstruction; and GOLD COPD stages II, III, or IV. Patients with respiratory disorders other than COPD were excluded.

A group of 55 patients aged 45 to 75 years with COPD were enrolled. All subjects provided written consent. Inclusion criteria included a diagnosis of COPD ($FEV_1/FVC < 0.7$), stable on medical therapy, smoking history $>$ 10 years (current and ex-smokers), and ability to complete the questionnaires. Exclusion

criteria included concomitant anticoagulant (except aspirin) therapy or recent use of investigational drugs, alcohol abuse, medical conditions such as (but not limited to) prior lung surgery, ventilator dependence, asthma, New York Heart Association class 3 or 4 congestive heart failure, cirrhosis, end-stage renal disease requiring dialysis, uncontrolled diabetes, alpha-1 antitrypsin disease, rheumatoid arthritis or other known significant inflammatory disorders, chronic respiratory failure (defined as partial pressure of oxygen < 60 mm Hg), right-sided heart failure, recent infections (within 21 days), pregnancy, and hospitalization for COPD exacerbation within 3 months.

Data Collection

Each subject participated in up to 5 study sessions. The duration of each subject's participation from screening to last followup telephone call was 3 years and a total of 7 visits. Data from the initial visit were used for this analysis.

Health-Related Quality of Life was assessed with generic and disease-specific quality-of-life questionnaires.[14,21] The SF-36 consists of 36 questions that cover 9 health domains, physical and social functioning, physical and emotional role limitations, mental health, pain index, vitality, general health perceptions, and health transitions. Scores for each domain range from 0 to 100, with the higher scores indicating better functioning. The SGRQ consists of 76 items addressing the effect of respiratory disease on HRQOL. A composite score and 3 domain scores for symptoms, activity, and impact range from 0% to 100%, with higher scores indicating worse impairment.

Patients performed pulmonary function testing following American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.[22] The symptom-limited noninvasive cardiopulmonary exercise test was performed following ATS/American College of Chest Physicians standards.[23] Exercise tolerance was measured using the 6MWD testing following the recommendations of the ATS.[24] The longer of 2 walk tests measured with a 30-minute rest in between was used for analysis.

The selection of biomarkers was based on a review of the literature and their biological plausibility. For instance, plasma C-reactive protein (CRP),[25] fibrinogen,[26] and interleukin 6 (IL-6)[27] have been well studied and associated with poor clinical outcomes and mortality in COPD. The levels of IL-6,[7] tumor necrosis factor α (TNF-α)[4] and surfactant protein D (SP-D)[28] are associated with disease-specific HRQOL. In addition, relationships between functional limitations and IL-6, IL-8, and TNF-α have also been described.[7] As proteolytic enzyme activity and lung epithelial injury have been implicated in the development and progression of COPD, we included assays for matrix metalloproteinases[29] and Clara cell secretory protein 16 (CC-16)[30] in our analysis. Therefore, our biomarker panel included IL-6, IL-8, CRP, SP-D, TNF-α, matrix metalloproteinases, and CC-16.

For biomarker analysis, the blood was allowed to clot for 30 minutes and serum was obtained by centrifugation at 1500 *g* for 10 to 15 minutes. For plasma preparation, whole blood was collected into vacutainer tubes containing EDTA. Plasma was obtained by centrifugation at 2000 *g* for 10 to 15 minutes. Serum and plasma samples were stored at −80°C until analyzed. With the exception of fibrinogen, all biomarkers, including SP-D and CC-16, were measured using validated immunoassays (Aushon Biosystems, Inc, Billerica, MA). Fibrinogen was measured using an immunoturbidometric assay validated for use with EDTA plasma (K-ASSAY fibrinogen test, Kamiya Biomedical Co, Seattle, WA). Assays were performed in duplicate to allow assessment of assay variation.

Statistical Analysis

Descriptive statistics were performed for all data. Categorical data were summarized using frequency counts and percentages, while continuous data were summarized using means and standard deviations. The number of missing data points was low and missing values were not imputed. However, for biomarkers with missing values due to the concentration being below the limit of detection of the assay, values were imputed to be half the limit of detection.

Comparisons of means or frequencies between groups were performed using a *t* test or a Cochran-Mantel-Haenszel test, respectively. The relationship between pairs of continuous variables was assessed using linear regression and the Pearson correlation coefficient was used to express strength and direction of the relationship. Differences between groups and tests of association were declared significant at the 5% level. There was no adjustment for multiple testing.

RESULTS

Subject Characteristics

The baseline characteristics of the 55 COPD subjects (25 women and 34 men) are summarized in Table 1. The mean age was 63 years and the mean BMI was 29 kg/m^2. As compared with patients able to walk > 350 m during testing, COPD patients who walked < 350 m had more significant airflow obstruction with a mean $FEV_1 = 0.96$ L (34% predicted), lower diffusing capacity for carbon monoxide (48% predicted) and

Table 1 • Characteristics of Patients With COPD Stratified by 6-Minute Walking Distance[a]

	6MWD < 350 m	6MWD > 350 m	*P* Value
Patients, n	17	38	
Age, y	64 (59-69)	62 (59-65)	.42
Female sex, n	10	15	.19
BMI, kg/m^2	30.3 (28.1-32.5)	27.8 (25.8-29.8)	.12
Smoking history, pack years	58 (44-72)	53 (41-64)	.54
Current smoker, n	7	17	.81
CAD, n	0	3	NS
Congestive heart failure, n	0	1	NS
Diabetes mellitus, n	6	1	<.01
FEV_1, L, mean	0.96 (0.71-1.21)	1.42 (1.22-1.62)	<.01
FEV_1, % predicted	34 (26-42)	46 (41-52)	.01
FEV_1/FVC	54 (46-61)	57 (51-63)	.49
RV, L	3.9 (3.2-4.7)	3.8 (3.4-4.2)	.8
FRC, L	4.5 (3.7-5.2)	4.8 (4.3-5.2)	.51
TLC, L	6.5 (5.9-7.2)	7.2 (6.6-7.8)	.2
DLCO, uncorrected, mL/min/mmHg	10.27 (7.88-12.65)	13.83 (12.33-15.33)	.01
DLCO, % predicted	48 (39-57)	61 (56-66)	<.01
$\dot{V}O_2$peak, % predicted	54 (46-61)	63 (57-69)	.08
VE/MVV, %	71 (65-78)	69 (62-77)	.74
HRR, %	46 (34-58)	69 (62-76)	<.01
Pre-SpO_2, %	92 (89-95)	95 (94-96)	<.01
Peak-SpO_2, %	90 (87-93)	94 (93-95)	<.01

Abbreviations: DLCO, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FRC, functional residual capacity; FVC, forced vital capacity; HRR, heart rate recovery; O_2 pulse, oxygen uptake per heart beat (approximates stroke volume); NS, nonsignificant; RV, residual volume; SpO_2, peripheral arterial oxygen saturation; TLC, total lung capacity; VE/MVV is the maximum minute ventilation during exercise relative to minimum voluntary ventilation at rest (ratio > 80% suggests a pulmonary limitation to exercise); $\dot{V}O_2$peak, peak oxygen uptake; 6MWD, 6-minute walk distance.

[a]Continuous variables are expressed as mean (95% CI).

lower resting and peak oxygen saturations. Total lung capacity was similar among all patients with COPD.

Relationship Between HRQOL Domains and Functional Status in COPD Subjects Walking < 350 m

The analysis comparing the HRQOL domains in COPD patients able to walk greater than or less than 350 m is shown in Figure 1. St. George's Respiratory Questionnaire scores for all subgroups were on average 8 points higher in COPD patients who walked < 350 m during the 6-minute walk test, compared with COPD patients able to walk > 350 m; although only the score in the activity domain was significantly different between the groups ($P = .02$). The score in the SF-36 domain of physical functioning was significantly different ($P < .01$) when comparing patients based on a 6MWD above or below 350 m, and there was a trend toward significance in the domain of physical role. On the contrary, scores in the domains of mental health, emotional role, vitality, and pain were similar between groups, regardless of 6MWD achieved.

Relationship Between HRQOL and Biomarkers in COPD Patients Stratified by 6MWD

The association between HRQOL domains and biomarkers in COPD patients walking greater than or less than 350 m is shown in Table 2. Higher levels of serum IL-8 were associated with lower scores in SF-36 domains of emotional role ($r = -0.717$; $P = .02$), bodily pain ($r = -0.662$; $P = .02$), general pain ($r = -0.741$; $P = .01$), vitality ($r = -0.748$; $P = .01$), and mental health ($r = -0.789$; $P = .01$) in COPD patients

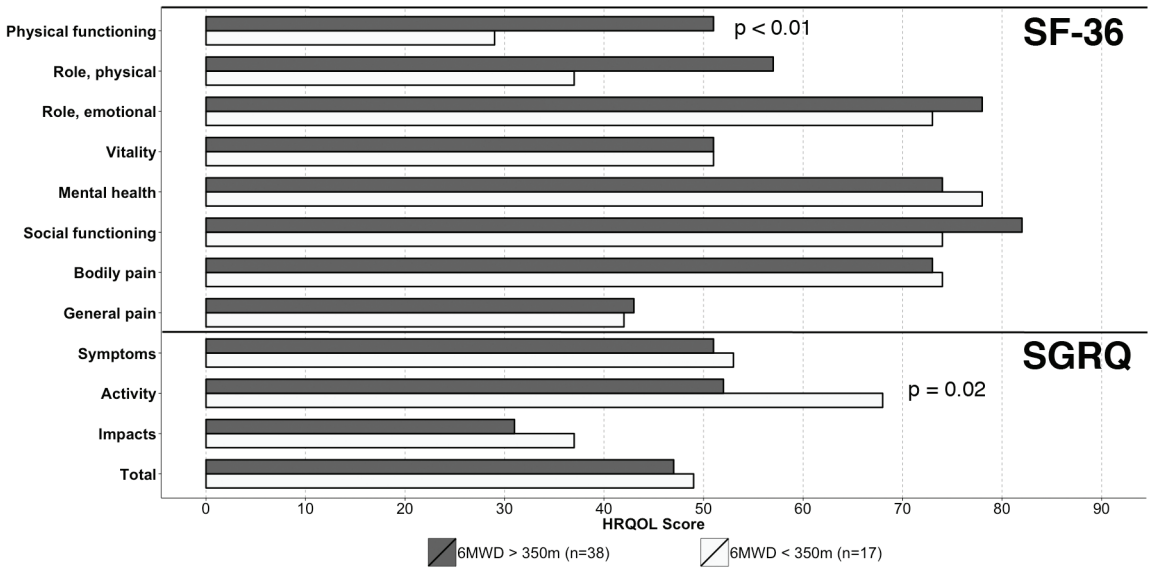

Figure 1. SF-36 and SGRQ scores in COPD subjects stratified by 6MWD. Abbreviations: HRQOL, health-related quality of life; SF-36, Medical Outcomes short-form-36; SGRQ, St. George's Respiratory Questionnaire; 6MWT, 6-Minute Walk Test.

with a 6MWD < 350 m. There was no significant correlation between IL-8 levels and any domains of the SGRQ in this group.

In contrast, SP-D levels were significantly associated with higher SF-36 scores in the domains of general pain ($r = 0.417$; $P = .05$), vitality ($r = 0.425$; $P = .05$), and social functioning ($r = 0.441$; $P = .04$) and in all SGRQ domains except "activity" in COPD patients walking > 350 m. In the absence of stratification by walking distance, there was no significant association between any biomarkers and the SF-36 domains of physical functioning and physical role across all patients.

DISCUSSION

This prospective study of patients with COPD provides 2 novel findings. First, in functionally limited COPD patients who walk < 350 m during the 6MWD test, the physical domains of the SF-36 and SGRQ were significantly associated with 6MWD and constituted the only important difference in HRQOL compared with patients who walked > 350 m. Second, inflammatory markers were not associated with HRQOL domains of physical functioning and physical role suggesting that the physical differences between COPD patients who were able to walk < 350 m and their counterparts with better functional capacity may not be driven by systemic inflammation. However, the inflammatory marker IL-8 was associated with emotional role, pain, vitality, and mental health in those with 6MWD < 350 m, suggesting that inflammation may play a role in nonphysical domains of well-being that impact performance on this functional field test.

The 6MWD is an excellent indicator of physical function and therapeutic response in patients with COPD[31] and has gained wide acceptance given its simplicity and standardization.[32] Specifically, the 6MWD has been used effectively to evaluate the effect of pulmonary rehabilitation and changes in exercise capacity.[33] A recent systematic review from the ERS and the ATS concluded that the 6MWD responsiveness was high, especially to interventions that included exercise training.[34] This test has also been shown to provide prognostic information in COPD, as a more reliable predictor of mortality in patients completing rehabilitation[35] than other tests such as spirometry.[34] In spite of this strong evidence for the 6MWD as a robust test of functional capacity and prognosis, there are no studies evaluating the relationship between the distances walked by patients with COPD and biomarkers, using the 6MWD threshold that has been found to predict outcomes.

Two large studies and a systematic review demonstrated that a 6MWD of 350 m separates COPD patients at an increased risk for death and supports the existence of a curvilinear association between 6MWD and mortality, where the relationship is linear below that threshold.[2,8,34] This asymptotic relationship may help explain the modest associations that have been observed between 6MWD as a continuous variable and both the SGRQ[36,37] and SF-36[15] scores. A prior study of the ECLIPSE cohort revealed significantly higher total SGRQ scores between COPD patients with a 6MWD < 350 m compared with their

Table 2 • Relationship Between Serum Biomarkers and Health Status in COPD Patients According to 6-Minute Walk Distance[a]

	IL-6 Pearson *r* (*P* Value)		IL-8 Pearson *r* (*P* Value)		CRP Pearson *r* (*P* Value)		Fibrinogen Pearson *r* (*P* Value)		SP-D Pearson *r* (*P* Value)		TNF-α Pearson *r* (*P* Value)		MMP-9 Pearson *r* (*P* Value)		CC-16 Pearson *r* (*P* Value)	
6MWD, m	**<350**	**>350**	**<350**	**>350**	**<350**	**>350**	**<350**	**>350**	**<350**	**>350**	**<350**	**>350**	**<350**	**>350**	**<350**	**>350**
SF-36																
Physical function	0.516 (.13)	−0.304 (.16)	−0.202 (.58)	−0.232 (.29)	0.217 (.48)	−0.011 (.95)	0.391 (.19)	−0.005 (.98)	0.012 (.98)	0.322 (.14)	0.180 (.62)	0.121 (.58)	−0.425 (.22)	−0.295 (.17)	0.135 (.73)	0.191 (.39)
Role, physical	0.147 (.69)	−0.009 (.97)	−0.539 (.11)	0.249 (.25)	−0.273 (.37)	−0.112 (.54)	0.090 (.77)	−0.052 (.77)	0.202 (.60)	0.375 (.09)	0.029 (.94)	0.198 (.36)	0.038 (.92)	0.039 (.86)	−0.357 (.35)	0.140 (.53)
Role, emotional	−0.114 (.75)	0.196 (.37)	**−0.717 (.02)**	0.129 (.56)	0.248 (.41)	−0.205 (.25)	0.199 (.51)	−0.088 (.63)	0.302 (.43)	0.300 (.18)	−0.068 (.85)	0.079 (.72)	0.086 (.81)	−0.289 (0.18)	−0.182 (.64)	0.229 (.30)
Bodily pain	−0.342 (.33)	0.362 (.09)	**−0.662 (.04)**	0.284 (.19)	0.217 (.48)	−0.199 (.27)	0.384 (.20)	0.274 (.12)	0.405 (.28)	0.394 (.07)	−0.334 (.35)	0.127 (.56)	−0.092 (.80)	−0.244 (.26)	0.427 (.25)	0.366 (.09)
General pain	0.267 (.46)	−0.215 (.33)	**−0.741 (.01)**	0.052 (.81)	0.209 (.49)	−0.125 (.49)	0.245 (.42)	−0.350 (.05)	0.120 (.76)	**0.417 (.05)**	0.084 (.82)	0.141 (.52)	−0.130 (.72)	−0.274 (.21)	0.219 (.57)	0.075 (.74)
Vitality	0.120 (.74)	−0.232 (.29)	**−0.748 (.01)**	−0.063 (.77)	0.403 (.17)	−0.342 (.05)	0.528 (.06)	−0.509 (.00)	0.393 (.29)	**0.425 (.05)**	−0.055 (.88)	0.103 (.64)	0.173 (.63)	−0.024 (.91)	0.270 (.48)	0.282 (.20)
Social function	−0.605 (.06)	0.190 (.39)	−0.403 (.25)	0.194 (.38)	0.399 (.18)	−0.351 (.05)	0.491 (.09)	−0.094 (.60)	**0.679 (.04)**	**0.441 (.04)**	−0.608 (.06)	0.171 (.44)	0.238 (.51)	−0.043 (.84)	0.149 (.70)	0.423 (.05)
Mental health	−0.412 (.24)	−0.076 (.73)	**−0.789 (.01)**	−0.110 (.62)	0.318 (.29)	−0.136 (.45)	0.384 (.19)	−0.266 (.13)	0.508 (.16)	0.363 (.10)	−0.439 (.20)	0.195 (.37)	0.103 (.78)	−0.318 (.14)	0.355 (.35)	0.295 (.18)
SGRQ																
Symptoms	−0.491 (.15)	0.286 (.19)	0.447 (.20)	−0.033 (.88)	−0.427 (.15)	0.235 (.19)	−0.270 (.37)	0.332 (.06)	0.199 (.61)	**−0.634 (.00)**	−0.618 (.06)	−0.110 (.62)	0.104 (.78)	0.280 (.20)	−0.330 (.39)	−0.291 (.19)
Activity	**−0.723 (.02)**	0.236 (.29)	0.088 (.81)	0.078 (.73)	−0.182 (.55)	−0.004 (.98)	−0.294 (.33)	0.256 (.16)	0.163 (.68)	−0.313 (.17)	−0.448 (.19)	−0.113 (.62)	0.083 (.82)	0.398 (.07)	0.035 (.93)	−0.032 (.89)
Impacts	−0.493 (.15)	0.167 (.44)	0.407 (.24)	−0.013 (.95)	−0.253 (.41)	0.133 (.46)	−0.283 (.35)	0.282 (.11)	−0.007 (.98)	**−0.463 (.03)**	−0.415 (.23)	−0.156 (.48)	−0.111 (.76)	0.235 (.28)	0.103 (.79)	−0.209 (.35)
Total	−0.608 (.06)	0.219 (.33)	0.351 (.32)	0.005 (.98)	−0.273 (.37)	0.144 (.44)	−0.307 (.31)	0.350 (.05)	0.075 (.85)	**−0.450 (.04)**	−0.493 (.15)	−0.151 (.50)	−0.027 (.94)	0.333 (.13)	0.035 (.93)	−0.176 (.45)

Abbreviations: CC16, Clara cell protein; CRP, C-reactive protein; IL-6, interleukin-6; IL-8, interleukin 8; MMP, matrix metalloproteinase; SF-36, Medical Outcomes SF-36 questionnaire; SGRQ, St. George's Respiratory Questionnaire; SPD, surfactant-associated protein-D; TNF-α, tumor necrosis factor-alpha; 6MWD, 6-minute walk distance; SP-D, surfactant protein D.

[a]Bold font cells represent correlations that were significant at $P \leq .05$. For the SF-36, higher scores indicate better functioning. Therefore, negative correlations between domains of the SF-36 and IL-8 reflect higher IL-8 levels found in patients with lower SF-36 scores, or poor functioning. Conversely, for the SGRQ, higher scores indicate worse impairment. Therefore, negative correlation correlations between domains of SGRQ and SP-D reflect higher SP-D levels found in patients with lower SGRQ scores, or better functioning.

more functional counterparts, regardless of GOLD stage.[2] However, differences in the individual domains of the disease-specific SGRQ and more generic HRQOL measures have never been examined. When we examined the HRQOL measures in this severely functionally limited group of COPD patients at increased risk of mortality, we found that both the SF-36 and SGRQ questionnaires accurately reflect the decrement in functional status. Indeed, the SGRQ activity domain and the SF-36 domain of physical functioning were significantly different between COPD patients who walked less than or greater than 350 m, suggesting that this difference in functional capacity is reflected similarly within both instruments.

In this study, we also explored the relationship between levels of biomarkers and HRQOL measures in these 2 COPD patient populations (6MWD $>$ and $<$ 350 m) in an effort to elucidate possible biological mechanisms behind the difference in HRQOL outcomes. In prior studies of COPD patients, biomarkers such as serum IL-6, IL-16, and TNF-α have been independently associated with 6MWD as a continuous variable and total SGRQ scores.[7] Interleukin 6,[27] fibrinogen,[26] and CRP[27,38] have also been associated with disease severity and poor outcomes. However, no studies to our knowledge have examined the relationship between HRQOL measures and serum biomarker levels in these functionally distinct groups.

In this study, there were no associations between any biomarkers and the SF-36 domains of physical functioning and physical role in either group, suggesting that a systemic inflammatory process may not be contributing directly to physical and functional limitations. However, in COPD patients who walked $<$ 350 m, the IL-8 level was inversely associated with SF-36 domains of emotional role, bodily pain, general pain, vitality, and mental health. Prior literature does support the association of inflammation with psychological changes such as depression in COPD, although few have examined IL-8.[39-41] Given the absence of elevation in other inflammatory markers in this population, IL-8 may play a more important role in psychological limitations and perceptions of pain than previously recognized. The association between higher levels of SP-D and HRQOL in patients who walked $>$ 350 m reflects this marker's association with fewer COPD exacerbations as observed in the large ECLIPSE cohort of COPD patients.[42]

This study has several limitations, including a limited sample size. Therefore, some findings lacking statistical significance may have been due to inadequate statistical power. Replication with a larger cohort would help solidify these findings. Second, the results are correlative in nature, limiting our ability to define causality. Interventional strategies in randomized trials evaluating the multiple domains here analyzed will yield more mechanistic insights. Third, we recognize that, as is commonly the case in health status research, we measured multiple functional domains and thus we used multiple comparisons in our statistical approach. As such, some of our significant findings may be due to chance alone. However, the results are not only biologically plausible but also clinically meaningful and can serve to generate further research in this field. We certainly encourage further efforts to define predictors of various patient-centered outcomes and their relationship to biological processes.

In summary, this study shows that in functionally limited COPD patients who walk $<$ 350 m during the 6MWD test, the physical domains of the SF-36 and SGRQ are important measures of HRQOL that reflect the relationship between functional status and HRQOL. Also, the lack of association between inflammatory markers and the HRQOL domains related to physical functioning and physical role suggest that the functional difference between COPD patients who were able to walk $<$ 350 m and their counterparts with better functional capacity may not be driven by systemic inflammation. However, IL-8 is inversely correlated to scores in nonphysical SF-36 domains of emotional role, pain, vitality, and mental health in those who walk $<$ 350 m, suggesting that IL-8 may play a more important role in psychological limitations and perceptions of pain than previously recognized. There is a need for more studies relating patient-centered outcomes with potential biological mechanisms.

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