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Frailty: A global measure of the multisystem impact of COPD.

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### **Holistic**

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**ABSTRACT**

Chronic obstructive pulmonary disease (COPD) is a multisystem disease, which resembles the accumulation of multiple impairments seen in aging. A Comprehensive Geriatric Assessment (CGA) captures multisystem deficits, from which a frailty index (FI) can be derived. We hypothesised that patients with COPD would be frailer than a comparator group free from respiratory disease.

In this cross-sectional analysis, the CGA questionnaire was completed and used to derive an FI in 520 patients diagnosed with COPD and 150 comparators. All subjects were assessed for lung function, body composition, 6 minute walking distance (6MWD) and handgrip strength. Patients completed validated questionnaires on health related quality of life and respiratory symptoms.

Patients and comparators were similar in age, gender and BMI but patients had a greater mean $\pm$ SD FI 0.16 $\pm$ 0.08 than comparators 0.05 $\pm$ 0.03. In patients, a stepwise linear regression 6MWD ( $\beta$ =-0.43), number of comorbidities ( $\beta$ = -0.38), handgrip ( $\beta$ = -0.11) and number of exacerbations ( $\beta$ = 0.11) were predictors of frailty (all  $p$ <0.01).

This large study suggests patients with COPD are frailer than comparators. The FI derived from the CGA captures the deterioration of multiple systems in COPD, and provides an overview of impairments which may identify individuals at increased risk of morbidity and mortality in COPD.

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the few major chronic conditions increasing in prevalence. The defining feature of COPD is impaired lung function, but extra-pulmonary comorbidities contribute to reduced health related quality of life (HRQoL), increased morbidity and mortality risk.<sup>1,2</sup> Quantifying multimorbidity is challenging as current routine clinical assessments do not take account of comorbidities. However, a scoring system based on BMI, airflow obstruction, dyspnoea and exercise (BODE index) and comorbidities predicted mortality risk over a four year period.<sup>1</sup>

Comorbidities represent deficits in individual physiological systems and resemble the accumulation of deficits in natural aging, which may result in frailty.<sup>3,4</sup> Frailty is associated with aging and manifests as failure to respond to external stresses and maintain homeostasis.<sup>5</sup> Frailty better predicts adverse outcomes than age, independent of co-existing medical conditions.<sup>6</sup> The similarities between the accumulation of deficits in aging and multiple comorbidities in COPD, suggests that frailty is likely to occur in COPD, and be related to increased morbidity.<sup>3</sup> Studies in a range of general populations and COPD patients have produced an inconsistent prevalence of frailty in COPD <sup>7,8</sup> ranging from 10% frail and 51% intermediate frail, in the Rotterdam study <sup>9</sup> to 57.8% frail in physician diagnosed COPD,<sup>10</sup> and 25.6% in patients referred for pulmonary rehabilitation.<sup>8</sup> A recent study reported 21% frailty in a Japanese COPD cohort.<sup>11</sup> In addition to various populations studied, there were differences in study design, methods to assess frailty and lack of appropriate population controls.<sup>12, 13</sup>

There are a number of validated tools to assess frailty.<sup>3, 12, 13</sup> The key ones in current use include: 1) the phenotypic definition based on the presence of  $\geq 3$  of 5 deficits including; walking speed, handgrip strength, activity levels, weight loss and exhaustion,<sup>3</sup> which has been criticised for not grading or specifying degrees of frailty. 2) To consider frailty as a multidimensional, risk state quantified by the number, rather than the nature of physiological deficits.<sup>3, 6, 13</sup> Using a widely validated questionnaire to capture information on health status and function, the Comprehensive Geriatric Assessment (CGA), a frailty Index (FI- CGA) can be derived.<sup>14</sup> In many populations this operationalised approach to defining and quantifying frailty has demonstrated that accumulated deficits, are a stronger predictor of mortality than chronological age.<sup>13</sup> In geriatric medicine, the FI- CGA is used clinically to assess the multisystem impacts of aging and indicate premature aging.<sup>6, 14</sup>

Although there have been other studies of frailty in COPD, to our knowledge, this is the first to explore and report frailty using the CGA, in a well-characterised population of community

dwelling patients with COPD, along with a group of comparators similar in age and sex from the same community. We hypothesised that frailty occurs in COPD based on the FI-CGA assessment, and that patients would be more frail than comparators independent of age which may indicate an accelerated and premature aging process in COPD.

## **METHODS**

### **Study design and participants**

This cross-sectional analysis included community-based patients with COPD, confirmed by spirometry at entry, and comparators (current or ex-smokers free from respiratory disease). Participants were drawn from the prospective Assessment of Risk in Chronic Airways Disease Evaluation (ARCADE) study, (Clinical Trials.gov, NCT01656421)<sup>15</sup> and included all participants who completed the CGA. All participants were clinically stable, not having received or oral corticosteroids in the previous 4 weeks prior to recruitment. Exclusions included inflammatory disease such as rheumatoid arthritis, oral maintenance corticosteroids, inflammatory bowel syndrome and long-term oxygen therapy. The exclusions were to study a sample of patients representative of the general COPD population, without significant impairment due to recent exacerbation or use of LTOT.

Participants were recruited from respiratory outpatient clinics, pulmonary rehabilitation, smoking cessation referrals, general practice databases and previous participants in respiratory research at Cardiff University. Comparators were recruited, based on being a current or past smoker, from primary and smoking cessation clinics, as well as past volunteers in research and partners of patients with COPD, in an attempt to standardise socioeconomic differences. All participants gave written informed consent and the study had approval from the South East Wales Research Ethics Committee.

### **Frailty and questionnaires relating to COPD**

All participants completed a modified version of the CGA questionnaire,<sup>4</sup> specific to community dwelling individuals was administered to all participants. The CGA collects data on self-rated health, psychological wellbeing, mobility, function, nutritional status, medications and co-morbidities which are coded to reflect deficits (Supplement 1). In community-dwelling participants of the Canadian Study of Health and Ageing, the FI-CGA was a valid and reliable means of quantifying health status, stratifying patients' risk of institutionalisation and death.<sup>16</sup> The CGA was modified by removal of the components specific to hospital admission and data was collected by a researcher-administered questionnaire, which took less than 10 minutes to complete. The FI-CGA was calculated by dividing the total number of CGA deficits by the maximum possible score of 61.

Patients with COPD completed the St. George's Respiratory Questionnaire (SGRQ) a validated disease specific measure of HRQoL, scores ranging from 0 to 100, with high scores representing worse status,<sup>17</sup> and the COPD Assessment Test (CAT), scored 0-40 with high scores indicating more symptoms.<sup>18</sup> Patients reported the number of respiratory exacerbations (defined as requirement for antibiotic or oral corticosteroid therapy) per year<sup>19</sup> and the number of previously diagnosed comorbidities in patients and comparators were also self-reported using a standardised questionnaire which was verified by researcher at the clinical assessment. Infrequent exacerbators were defined as <2 in the previous year, while frequent exacerbators as  $\geq 2$ . Breathlessness was recorded using the modified Medical Research Council (mMRC) dyspnoea scale.

### **Lung function**

All participants performed spirometry (Vitalograph Alpha), to determine forced expiratory volume in one second (FEV<sub>1</sub>), forced vital capacity (FVC) and the FEV<sub>1</sub>:FVC ratio. A diagnosis of COPD was confirmed as post bronchodilator spirometry FEV<sub>1</sub>:FVC <0.70.<sup>19</sup> Patients were classified according to the combined assessment, GOLD A-D based on the CAT score.<sup>19</sup>

### **Body composition and physical performance**

Weight and body composition were measured barefoot in lightweight indoor clothing, fat percentage, fat free mass (Go, #79) and the body mass index (BMI kg/m<sup>2</sup>) were determined using a segmental bio-electrical impedance analyser (BC418 Tanita Corp, Tokyo). The FFM index was expressed as a height-squared ratio (FFMI) kg/m<sup>2</sup>. A stretch resistant tape measure was used to measure waist and hip circumference.

All participants completed the six minute walking distance (6MWD) test with pre-test resting heart rate and oxygen saturation by pulse oximetry.<sup>20</sup> Mean maximum handgrip strength, twice with each hand, was determined using a hand dynamometer (Takei, Japan).

### **Inflammation**

High sensitivity C-Reactive Protein (HsCRP) and fibrinogen were determined in venous blood by standard procedures (University Hospital of Wales, Biochemistry).

### **Data Analysis**

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS, Chicago, USA), version 18.0. Results are presented as mean  $\pm$  standard deviation (SD), geometric mean for  $\log_{10}$  transformed data and median, interquartile range [IQR]. Analyses included the independent t-test, Wilcoxon test, Pearson's (r) or Spearman's ( $r_s$ ) correlation, and stepwise multiple regression.

## **RESULTS**

### **Participant characteristics**

The FI was greater in the patients  $0.16 \pm 0.08$  than the comparators  $0.05 \pm 0.03$ , ( $p < 0.001$ ). Patients also had poorer lung function FEV<sub>1</sub>, FVC and FEV<sub>1</sub>/FVC, greater smoking history, larger waist circumference, lower handgrip and 6MWD, as well as greater inflammation (HsCRP $\log_{10}$  and fibrinogen). However, patients and comparators were similar in age, gender, BMI and body composition (Table 1).

Female patients had greater FI  $0.17 \pm 0.09$ , than males  $0.14 \pm 0.09$ , ( $p < 0.001$ ) and female comparators had greater FI  $0.06 \pm 0.04$  than males  $0.04 \pm 0.03$ .

### **Frailty and characteristics of COPD**

Based on the upper 90<sup>th</sup> centile FI for comparators (0.09) as a cut-off for frailty, 76% of the patients were frail and 13% of comparators were frail. However, using the upper 50% CI of the age adjusted cut-off for frailty from the SHARE cohort (a large general, unselected, age related European population) 28% (n=143) of patients and 0% of comparators were frail.

Frail patients (according to SHARE) were younger, had poorer lung function, greater BMI, waist and fat percentage as well as poorer handgrip and 6MWD compared to non-frail patients. Frail patients also had greater inflammation (IL-6 and HsCRP) and more exacerbations, symptoms (CAT) and poorer quality (SGRQ) all  $p < 0.05$  (Table 1).

### **Medical History**

Patients with COPD had more comorbidities and reported more medications than comparators ( $p < 0.05$ ). The most commonly reported comorbidity in both patients and comparators was hypertension and hypercholesterolaemia.

Frail patients with COPD had more comorbidities including a greater proportion reporting cardiovascular disorders as well as diabetes, osteoporosis and osteoarthritis and more medications than non-frail patients with COPD ( $p < 0.05$ ) (Table 2). This remained after adjustment of age and the number of comorbidities: frail  $0.18 \pm 0.05$  versus non-frail  $0.14 \pm 0.04$  ( $p < 0.05$ ). Of the patients, frequent exacerbators ( $>2/\text{year}$ )  $n=310$ , had a greater mean FI  $0.19 \pm 0.09$  than infrequent exacerbations, ( $0-1/\text{year}$ )  $n=210$ ,  $0.15 \pm 0.08$ , and both had a greater FI than that of the comparator group,  $0.05 \pm 0.04$  ( $p < 0.001$ ).

Using the SHARE cut-off for frailty for each decade,<sup>21</sup> mean FI and the percentage of frail patients differed across: age categories (Figure 1a), MRC dyspnoea (Figure 1b), GOLD 1-4 (Figure 1c), and classified according to the Gold 1-4 and using the combined assessment of COPD A-D using the CAT score (Figure 1d) (all  $p < 0.05$ ). Age and gender did not differ across the classifications and only the number of comorbidities differed across the gold categories A-D.

When adjusted statistically for the number of comorbidities, the number of patients classified as frail according to SHARE reduced to  $n=75$ . The proportion of frail patients no longer differed across the mMRC, Gold1-4 or Gold A-D categories ( $p > 0.05$ ).

### **Relationships between Frailty Index and Participant Characteristics**

In COPD, FI was inversely related to FEV<sub>1</sub>%, handgrip and 6MWD. Measures of body composition (BMI, waist circumference and fat percentage) and inflammation (HsCRP and fibrinogen) were directly related to FI, along with disease specific questionnaires as well as the number of comorbidities and exacerbations per year (all  $p < 0.01$ ) (Table 3).

In patients, a stepwise linear regression with the FI as a dependent variable, FEV<sub>1</sub>%, BMI, handgrip, 6MWD, number of exacerbations per year, number of comorbidities and fibrinogen<sub>log10</sub>, as were included as independent variables, based on the results of correlations between CGA and the independent variables. This produced a significant model which explained 51% of the variance of frailty. 6MWD ( $\beta = -0.43$ ), was the primary predictor, followed by number of comorbidities ( $\beta = -0.38$ ), handgrip ( $\beta = -0.11$ ) and number of exacerbations ( $\beta = 0.11$ ) (all  $p < 0.01$ ). In comparators, number of comorbidities ( $\beta = -0.432$ ), 6MWD ( $\beta = -2.33$ ) and BMI ( $\beta = 0.22$ ) explained 38% of the variance of frailty ( $p < 0.01$ ).

In frail patients, the FI was related to BMI ( $r = 0.12$ ), fat mass ( $r = 0.13$ ), waist ( $r = 0.24$ ), HGS ( $r = -0.26$ ), 6MWD ( $r = -0.46$ ), number of exacerbations ( $r_s = 0.14$ ), SGRQ ( $r_s = 0.48$ ) and CAT ( $r_s = 0.45$ ) (all  $p < 0.05$ ), but not inflammation.

## DISCUSSION

In this study, patients with COPD were frailer than a comparator group, similar in age, gender and BMI but free from respiratory disease, and as demonstrated by their greater number of deficits measured as part of the CGA and higher FI score. In our female patients and comparators, the FI was greater than in their counterpart males, a similar relationship to that reported in the general population. The mean FI of females with COPD was greater than the reported FI of 0.15 for women over 65 years of age from general populations.<sup>22-24</sup>

The finding that 28% of our patients were frail based on the SHARE cohort is similar to a recent UK study in patients referred for pulmonary rehabilitation which reported that 26% of their patients were frail using a hybrid of Fried's criteria.<sup>8</sup> A recent study reported a prevalence of 21% frailty in patients with COPD using the Kihon Checklist.<sup>11</sup> These studies are lower than a UK population study where the reported prevalence of frailty was 57.8% in 70 COPD patients diagnosed on the basis of symptoms rather an objective measure of airways obstruction.<sup>10</sup> Unlike the latter study, our study population was unselected based on physician defined COPD with mandatory demonstration of airways obstruction at the time of entry to the ARCADE study<sup>15</sup> and hence provided a wider spectrum of disease severity and comorbidities which might account for the variation. Comparisons between this study and other studies<sup>7, 25</sup> are difficult due to different assessments of frailty and older study populations, which may not represent a typical COPD population. We used the validated CGA tool, which allowed our participants to be compared with other populations and has shown to be a predictor of outcomes than chronological age, disability and the need for healthcare support.<sup>6, 13</sup> Based on our own cut-off from frailty from our comparator group the percentage of frail patients was high (76%). This may be a result of low levels of frailty in comparators due to rigorous exclusion criteria and self-selection of volunteers for the study.

Using the SHARE cut-off frail patients had reduced physical capacity, greater systemic inflammation, worse symptoms and quality of life. Hence, frailty in COPD appears to have impacts and background mechanisms similar to those in natural aging where it is part of the spectrum of multimorbidity. There is likely to be two aspects of COPD interwoven with each other and frailty; the physiological processes of natural aging occurring in all individuals and the impact of COPD and its associated exacerbations and greater comorbidity levels.<sup>26</sup> Comorbidities in COPD are an important factor in the overall morbidity and mortality<sup>1</sup> and their interaction may be related to the greater systemic inflammatory state in aging – inflammaging – and the inflammatory surges during exacerbations superimposed on the background inflammatory state in COPD.<sup>27</sup> This speculation is supported by the association

between frailty and the number of comorbidities and number of exacerbations per year seen in this study. This potentially provides a testable explanation of premature aging in COPD.

Although, frailty in COPD was unrelated to chronological age, the proportion of frail patients differed across the age categories. Interestingly, patients aged 50-59 had greatest FI and the largest proportion of frail patients which could potentially be explained by a survival bias where frail patients fail to reach older age. In addition, frailty differed according to the disease severity classified by GOLD, in mild disease (Gold 1) 17% of patients were frail increasing to 34% frail in Gold 3 and 4. Patients in GOLD categories B&D with more symptoms as measured by the CAT score were frailer. These differences did not remain when frailty was adjusted for the number of comorbidities. This suggests that frailty may be as a result of increasing deficits which may occur prematurely even in mild COPD.

Frailty associated with components of body composition, including BMI, fat% and waist circumference. The linear relationship with BMI contrasts with the U-shaped distribution reported in the English Longitudinal Study of Ageing, but may be a consequence of small numbers of individuals with a low BMI.<sup>22</sup> In both COPD and natural aging, increases in fat and abdominal obesity have been closely linked to impaired physical function.<sup>28</sup> Increased fat mass and frailty in the older people has also been linked to increased levels of circulating inflammatory biomarkers.<sup>29</sup> Circulating CRP, an indicator of IL-6 activity, increases with age and has been linked to frailty and truncal obesity, independent of BMI, which may reflect the negative impact of chronic low grade systemic inflammation, a feature of COPD, on physical function and wellbeing.<sup>30</sup> Hence, our findings suggest frailty in COPD is a multifactorial function perhaps resulting in reduced physical function and quality of life.

In the present study frailty was predicted by physical function (6MWD and handgrip) and the number of exacerbations and co-morbidities. This aligns with previous studies where the non-linear association of frailty with age, functional dependence, and chronic disease has been established.<sup>3, 4, 6, 12-14, 31</sup> Although there are few specific studies in individual chronic diseases, such as reported here, in the Women's Health and Aging Studies, the risk of frailty increased with inflammatory comorbidities. This showed that the combination of pulmonary disease with anaemia carried a risk ratio of 5.57 compared with comparator participants who had fewer comorbidities.<sup>32</sup> A further study in this female cohort demonstrated that frailty was related non-linearly to the number of abnormal physiological systems, which resembles the impact of multiple comorbidities in COPD.<sup>12</sup> Such physiological deficits included loss of skeletal muscle mass (sarcopenia) and function, with progressive loss of capacity for

physical activity, loss of bone mineral density, increased systemic inflammation, reduction in HRQoL and increasing cardiovascular morbidity and mortality.<sup>22, 33, 34</sup>

Our patients with COPD were stable at the time of recruitment but had higher levels of inflammation (HsCRP and fibrinogen) than comparators, however the difference in fibrinogen between patients and comparators was small. The higher, than expected, levels of inflammation in comparators may be attributed to the age of the participants and potential presence of subclinical disease in some comparators despite being free from occult respiratory, cardiovascular disease or inflammatory conditions.<sup>35</sup> COPD is characterised by low-grade inflammation, both CRP and fibrinogen are acute phase proteins produced by the liver and have been associated with disease severity in COPD. However, fibrinogen is thought to be a more specific marker and has been associated with increased risk of exacerbation, hospitalisation and extra pulmonary manifestations.<sup>36</sup> The reported associations with frailty and aging, in many ways parallels findings in COPD, where systemic inflammation may be causal, compensatory or an epi-phenomenon.

This accumulation of deficits in COPD resembled the pattern of that occurring with aging healthy populations, potentially allowing the prediction of poor outcomes such as increased risk of falls, hospitalisation, residential care, reduced HRQoL, disability and increased mortality.<sup>3, 4, 6, 12-14, 31</sup> Although there are a number of ways of determining frailty, the CGA has the advantage of being a simple, rapid questionnaire that is applicable for all healthcare sectors.

### **Limitations of the study**

As with the majority of cross-sectional studies a limitation of the findings is that they may be influenced by bias, confounding and lack of causality. Although patients and comparators were similar they were not matched and there were differences the number of comorbidities between the groups. This, however, reflects the multisystem nature of the COPD, which is inherent to the disease. The ARCADE study was designed to describe a representative COPD group and a comparator group rather than a true controlled study. Frailty did not relate to age and after adjustment for smoking history, frailty remained elevated in COPD in line with Park's study where smoking was unrelated to frailty.<sup>10</sup> A limitation of the CGA questionnaire to determine frailty is that it relies on patient recall, nevertheless, many of the parameters could be verified by medical notes, physical assessment and carers.

### **CONCLUSION**

Patients with COPD were frailer than a comparator group of current or ex-smokers, independent of age. Frailty was predicted by the number of comorbidities and the number of exacerbations per year as well as physical function. This study highlights the need to take a holistic view of COPD to quantify the systemic nature of the disease. The CGA is a quick, simple and inexpensive questionnaire that provides a global assessment of COPD. The CGA may be a useful clinical tool to highlight the multisystem deficits of COPD, which could guide interventions, monitor disease processes and improve patient care.

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