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HEALTHY AGING RESEARCH

Cystic Fibrosis: Detecting frailty in an outpatient clinic

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Abstract

Background: With an ever-increasing life expectancy, the focus of cystic fibrosis (CF) care is shifting towards treating the premature appearance of age-related comorbidities associated with frailty. The purpose of this study was to assess whether frailty can be detected in CF patients in an outpatient setting, and whether it is associated with a poorer health status.

Methods: Physical frailty tests were conducted in a clinic setting as part of an annual review of health on consenting CF patients, using recognised frailty protocol.

Results: Frailty was found to be associated with older age and more comorbidities than among robust patients. Frail patients had significantly poorer lung function and received more intravenous antibiotics per annum than non-frail patients.

Conclusions: Our findings suggest that simple criteria can be incorporated into routine outpatient appointments to detect frailty among CF patients, found to correlate with poorer health.

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Introduction

The life expectancy of patients with cystic fibrosis (CF) is steadily improving in the UK; current evidence suggests a 50-year life expectancy for those born after the year 2000 [1]. With greater numbers of CF patients surviving into adulthood, several later complications have become increasingly prevalent among CF sufferers, ultimately leading to death [2]. The development of multiple comorbidities such as renal failure, heart disease and arthritis are also characteristic of the normal ageing process [3]. There is, therefore, an interest in monitoring the premature effects of ageing in the CF population.

Frailty has been described as a syndrome associated with increasing age, the presence of multiple comorbidities and general poor health [4]. While 'frail' is a term usually used to describe the elderly [5], a link between premature ageing, frailty and disease has been recognised in several chronic conditions. For instance, an association has been found between the incidence of comorbidities usually associated with advanced age, and HIV infection [3]. Additionally, previous reports have found frailty to be comparably prevalent among young adult survivors of cancer as within the general population of over 65 year olds [6, 7]. There is evidence to suggest that chronic disease patients suffering from additional comorbid conditions are the most likely to demonstrate signs of frailty [8].

Studies have shown that frailty is potentially detectable in a clinical setting, using non-invasive physical criteria to accurately monitor the frailty status of chronic disease sufferers of any age [6, 9]. Additionally, previous reports have found the use of frailty criteria to be an effective means of highlighting

chronic disease sufferers most at risk of mortality or health deterioration [8]. In this study we aim to determine whether patients exhibiting signs of frailty are more likely to suffer from a poorer health status than non-frail CF patients.

Methods

Study population

Eighteen CF patients were assessed according to frailty measures as part of their annual review appointments at University Hospital Llandough. Patient selection was randomised by the order of clinic appointments. All patients gave their consent to take part in the study.

Frailty criteria

Patients were assessed on their frailty levels based on the St. Jude cohort version [6] of the Fried criteria for frailty [4]. Patients meeting ≤1 of the criteria were deemed to be 'robust', while patients satisfying ≥2 of the frailty criteria were classified as having the 'frailty trait' (see Table 1 for details); a combination of the pre-frail (2 criteria) and frail (≥3 criteria) subgroups used in previous studies [4, 6].

Briefly, walk speed was assessed over 15 feet and compared to gender, age and height-matched averages [4, 10]. Hand-grip strength was determined using a digital dynamometer [11, 12] and Fat Free Mass Index (FFMI) was calculated using bioelectrical impedance analysis (BIA) [13]. Exhaustion and physical activity levels were evaluated using answers to the Medical Outcomes Survey (MOS) Short Form [14] and the National Health and Nutrition Examination Study (NHANES) questionnaire [15], respectively.

Health status

Data for each participant on forced expiratory volume percentage of predicted (FEV1 %); the presence of CF-related comorbidities including CF-related diabetes (CFRD), CF liver disease (CFLD), pancreatic insufficiency and osteoporosis; and the number of IV antibiotic courses received in the previous year were all collected using the clinic database.

Statistics

Statistical analyses were carried out using IBM SPSS Statistics 20 software. Chi-squared tests were used to detect associations between frailty and the presence of CF-related comorbidities. Other comparisons between patient groups were carried out using an independent samples t-test or, if the data were not normally distributed, a Mann-Whitney test. A significance level of $p < 0.05$ was used.

Results

Of the 18 participants in this study (10 male and 8 female), 9 (50%) were robust, while 9 (50%) met the combined "frailty trait" criteria with 4 being pre-frail (22%) and 5 frail (28%). Ages ranged between 19 and 56 years, with a cohort mean age of 31.3 ± 9.9 (SD).

The mean age in the frailty trait group (34.1 ± 11.4) was greater than that of the robust group (28.6 ± 7.8) (see Table 2). Moreover, the average age of the frail group (40.6 ± 10.9), excluding pre-frail patients, significantly exceeded that of the robust group ($p < 0.05$). No association between gender and frailty trait was observed in this study, with 50% of the male and 50% of the female participants fulfilling the frailty trait criteria.

The majority of patients with CFRD met the frailty trait criteria (75%) (Figure 1). Osteoporotic CF Patients were found to be significantly more likely to meet the frailty trait than robust criteria ($p < 0.05$), with 83% of patients with osteoporosis classified as frailty trait (Figure 1). The presence of multiple comorbidities among members of the robust and frailty trait groups is represented graphically in Figure 2. Patients in the frailty trait group were more likely than robust patients to suffer from two or more comorbidities although this was non-significant ($p = 0.148$).

The frequency of lung infections suffered in the last year requiring treatment was represented by the number of intravenous (IV) antibiotic courses patients received in that time. Frailty trait patients were found to have received significantly more courses of IV antibiotics per year than patients in the robust group ($p < 0.05$) (Table 2).

Table 1. Criteria used to identify frailty

Frailty criteria	Method
Fat Free Mass Index (FFMI)	Bioelectrical impedance analysis (BIA) was used to calculate fat free mass (FFM). FFM was divided by height squared to calculate FFMI. A low FFMI was defined as an FFMI below the fifth percentile value for the general population [13].
Exhaustion	Determined by a MOS Short Form score ≥ 1.3 standard deviations below the population mean [14].
Physical activity	Activity levels were measured by participant answers to a NHANES questionnaire [15]. Low activity levels were defined as an energy expenditure of < 383 Kcal/week for males and <270 Kcal/week for females [4].
Walk speed	The time taken to walk 15 feet was recorded. Any value ≥ 2 standard deviations below the height normalised, gender and age specific mean average was classified as slow [4].
Hand-grip strength	Hand-grip strength was compared to age and gender-specific averages [11]. Grip strength below 85% of the population average has been found to be most predictive of malnutrition in previous literature [12].

To test for an association between frailty and lung function in CF, frailty status was compared to FEV1%. Patients in the frailty trait group had a significantly lower mean FEV1% than those in the robust group ($p < 0.05$) (Table 2), suggesting poorer lung function among frailty trait patients (Figure 3).

Discussion

In this study, frailty was found to be associated with significantly poorer lung function (FEV1), which is widely regarded as a marker of CF severity [16]. Frailty trait patients also suffered from more CF-related comorbidities, required more frequent courses of IV antibiotics and were older than the robust CF population. This study supports the possibility of using clinic based frailty assessment criteria as a screening tool to identify CF patients who are most likely to suffer from future poor health, as has been explored in a number of other chronic conditions [6, 9]. Previous studies have found walk speed to be a useful method of assessing functional capacity in chronic obstructive pulmonary disease (COPD) [17], however, no previous study has compared frailty and health status in CF using recognised frailty measures.

Chronic inflammation in CF begins at a young age; CF infants exhibit raised inflammatory markers in their lungs within their first month of life [18]. Walston et al. explored the association between age-related inflammation and frailty, and discovered a correlation between raised inflammatory markers and physical frailty, even in the absence of comorbidities [18]. In COPD, chronic inflammation has been found to

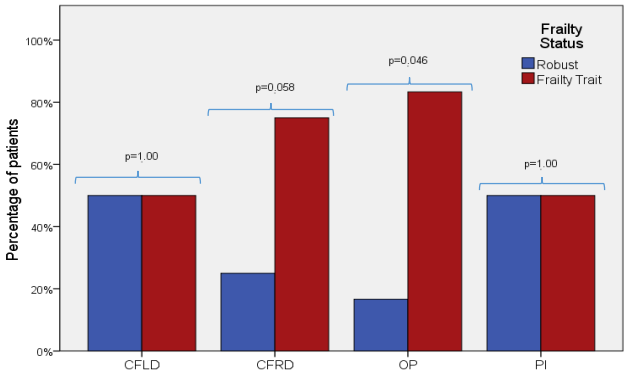

Figure 1. Comparison of the percentage of patients with each CF-related comorbidity who fulfil the robust or frailty trait criteria. Chi-squared test used to generate p-values. Abbreviations used: CFLD, CF liver disease; CFRD, CF-related diabetes; OP, osteoporosis; PI, pancreatic insufficiency.

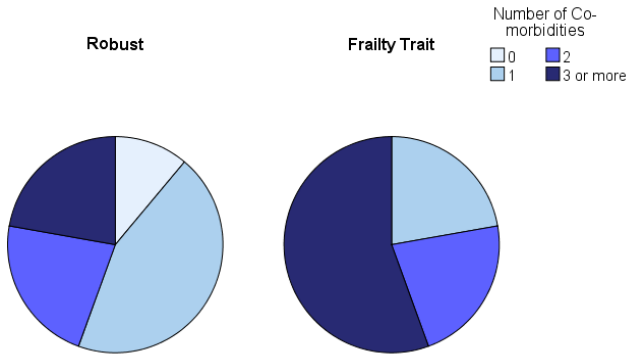

Figure 2. The proportions of robust and frailty trait patients with co-existing CF-related comorbidities.

Table 2. Comparison of lung function and the frequency of pulmonary infections.

Patient status	Mean age (± SD)	Mean no. of intravenous courses of antibiotics per year (± SD)	Mean FEV_1% of predicted (± SD)
Robust [n = 9]	28.6 (7.8)	1.3 (1.7)	86.7 (17.4)
Frailty trait [n = 9]	34.1 (11.4)	4.6 (2.1)	52.0 (26.3)
p-values	0.311	0.005	0.005

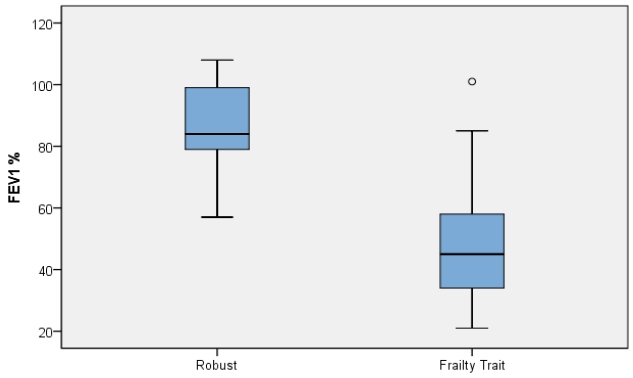

Figure 3. Comparison of the average and spread of FEV1 % values between the robust and frailty trait patient groups.

significantly shorten the lengths of telomeres [19], protective sequences found at the end of DNA strands that shorten with each cell cycle, leading to physiological dysfunction at the cellular level [20]. Therefore, frailty in CF may be a consequence of premature cellular aging as a result of inflammation-driven enhanced cell turnover.

The frailty criteria in this study were tailored to compare our patients against the age-matched general population, while conforming to the original framework defined by Fried et al. [4]. As a result, our study detected a similar proportion of truly frail CF subjects (28%) as other studies have found in older populations of chronic disease sufferers [9, 21]. This suggests that the alterations we made to the frailty criteria in order to account for a younger population group, have allowed our study to be comparable to previous literature.

In this study, because of the limited population size available to us, we were unable to compare the characteristics of frailty and pre-frailty. A longitudinal study is needed to determine whether, based on the associations between frailty and health status displayed in this study, frailty can be predictive of a poorer prognostic outlook in CF.

Conclusions

This preliminary study has demonstrated that frailty in CF is measurable in a clinic environment, and is associated with poorer health and more CF related comorbidities. Further research is required to determine whether the assessment of frailty in CF would allow the early detection of patients with worse prognoses, therefore allowing the implementation of more patient-specific treatment plans.

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