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Inflammation and frailty measures in older people

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Abstract

Inflammation in patients defined as frail by Fried's phenotypic definition may be related to sarcopenia. This study aimed to investigate inflammation in older patients across different frailty criteria. Frailty status was determined in 110 patients aged over 75 years (mean 83.9 years) according to function (dependent, intermediate, independent); Fried (three or more items of exhaustion, weight loss, slow walking speed, low handgrip strength, low physical activity) and Frailty Index (a measure of accumulated deficits). With increasing patient frailty as defined by function and by Fried phenotype, tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6) and C-reactive protein (CRP) increased significantly. Albumin was lowest in the frailest subjects by each definition. The greatest differences were seen between intermediate and dependent groups and between the pre-frail and frail. Adjustment for multiple covariates (age, sex, BMI category, smoking status, number of co-morbidities and number of prescribed medications) did not account for any of the observed differences in levels of inflammatory markers. The Frailty Index correlated significantly with log-transformed CRP ($r = 0.221$, $P < 0.05$), log-transformed IL-6 ($r = 0.369$, $P < 0.01$), TNF-α ($r = 0.379$, $P < 0.01$) and inversely with albumin ($r = -0.545$, $P < 0.01$). This study provides further evidence linking inflammation and frailty in older people, an association that seems consistent across different frailty measures.

Keywords: aged • 80 and over • frail elderly • inflammation • tumour necrosis factor-α • C-reactive protein • interleukin-6

Introduction

Frailty is an important concept in geriatric medicine and understanding its aetiology has become a fundamental aspiration of many researchers in the aging field [1]. Chronic inflammation may play a role in the pathophysiology of frailty [2, 3]. In older people, higher circulating levels of C-reactive protein (CRP) and interleukin-6 (IL-6) are inversely correlated with poor physical performance, and muscle weakness [4] and higher circulating levels of IL-6 predict the onset of disability [5]. Plasma levels of tumour necrosis factor-α (TNF-α) are strongly associated with death in community-dwelling subjects aged 72–92 years [6] and in centenarians [7].

Older people defined as frail by operational criteria defined by Fried *et al.* [8] exhibit evidence of increased inflammation, with higher levels of CRP [9] and IL-6 [10]. Fried's model has been praised for clinical reproducibility and coherency [11] and has been validated against adverse outcome in large population studies [8, 12]. However, it is based on physical parameters, whereas frailty is, arguably, a complex, multi-dimensional concept [13, 14]. Inflammation in Fried frail subjects may be related primarily to sarcopenia. In the study by Ferrucci *et al.* [5], most of the relationship between IL-6 and disability was accounted for by the detrimental effect on muscle strength. Furthermore, CRP, IL-6 and TNF-α receptor-2 levels are negatively correlated with rate of skeletal muscle protein synthesis [15], supporting the idea that low-grade inflammation is implicated in sarcopenia development [16].

Defining frailty is an area of ongoing debate [17] and application of different frailty criteria can give heterogeneous results in clinical practice [18]. The aim of the present study was to investigate inflammation in older patients according to varied frailty criteria.

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Materials and methods

Thirty institutionalized patients were recruited from Continuing Care wards on four different hospital sites in Cardiff, South Wales. These inpatients were dependent for activities of daily living, many were cognitively impaired and all met United Kingdom National Health Service Continuing Care criteria for ongoing nursing and medical needs [19]. Forty community-dwelling patients with a history of falls referred to Day Hospital for rehabilitation and 40 independent age-matched controls recruited from poster advertisements were also studied. These patients were defined, respectively, as dependent, intermediate and independent on a functional frailty spectrum [20–22].

Frailty indicators were measured in all subjects by a single observer (REH). History of weight loss, smoking status, medical diagnoses and drug history were self-reported by independent older people or documented from medical notes for intermediate or dependent patients. Use of anti-inflammatory drugs (non-steroidal anti-inflammatory drugs, cyclooxygenase-2 selective inhibitors and steroids) was noted. Height and weight were measured without shoes and with light clothing, height to the nearest 0.5 cm and weight to the nearest 0.1 kg. Height was estimated for dependent patients who could not stand from demi-span (measured in centimetres from the ring finger root to the sternal notch) and knee height, as described by Hickson and Frost [23]. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$ and BMI categorized as underweight ($<$20), recommended weight (20.0–24.9), overweight (25.0–29.9) or obese ($>$30.0) [24].

Participants were categorized according to Fried criteria [8] with cut-offs for positive frailty indicators set at the lowest 20% of the independent older group [25]: exhaustion (Energy and Vitality Score on Short-Form 36 of less than 40%), slow walking speed (6-min. walking distance of $\leq$210 m) and low handgrip strength. Weight loss ($\geq$10 pounds in preceding year) and low physical activity (a score of 1 or 2 out of 6 on a validated physical activity questionnaire [26]) were also Fried frailty indicators. Individuals with three or more components were defined as frail, one or two pre-frail and those with no positive frailty indicators as non-frail.

The Frailty Index measures frailty as a continuum rather than a dichotomous state, an approach summarized as 'the more things individuals have wrong with them, the higher the likelihood they will be frail' [27]. For this Frailty Index, a total of 30 variables were collected, including self-reported data, symptoms, co-morbidities and performance-based tests. Deficits were combined by adding them (1 for each deficit present, 0 if absent), and the Index was the total deficits as a proportion of those counted (*e.g.* 6/30 = 0.20).

Total white blood cell (WBC) count was obtained using a Coulter counter in the hospital-based laboratory and serum albumin and CRP measured (Abbott AEROSET system, Abbott Laboratories, Abbott Park, IL, USA). Plasma IL-6 and TNF-α were assayed by enzyme-linked immunosorbent assay using Quantikine® Colorimetric Kits. The optical densities were measured using a Bio-Rad Laboratories Ltd. Model 3550 Plate Reader (Hemel Hempstead, Herts, UK) and the mean of duplicate samples calculated.

The study was approved by the Local Research Ethics Committee. Written-informed consent was obtained from participants or, for patients who lacked capacity to give fully informed consent, assent was obtained from next of kin.

Data were analyzed using Stata 10.1 for UNIX. For normally distributed variables data were reported as mean and standard deviation and the statistical significance of differences across degrees of frailty was examined using analysis of variance. Variables with a skewed distribution (CRP and IL-6) were expressed as median, 25th and 75th percentiles. Log-transformed CRP values were roughly normally distributed and so were tested across frailty groups using analysis of variance. A significant proportion of participants had zero detectable IL-6 level and a log transformation was not possible in those cases. Therefore, we tested the proportion of cases with non-zero IL-6 across each group using logistic regression as well as the log-transformed IL-6 values in non-zero cases. Analyses were conducted univariately and after adjustment for age, sex, BMI, smoking, number of co-morbidities and number of prescribed medications. Correlations were explored using Pearson correlation coefficients.

Results

One hundred 10 patients were recruited [28]. Forty-four patients were male (40%) and all were Caucasian. No subjects showed signs of infection or were taking antibiotic treatment. Study population characteristics are shown in Table 1.

Prevalence of Fried frailty increased from 10% in independent older people to 72.5% in the intermediate function, Day Hospital group and 100% of dependent, Continuing Care patients. Eleven Day Hospital patients (27.5%) and 14 independent older people (35%) had 1–2 frailty indicators and were 'pre-frail'.

The Frailty Index increased significantly with increasing functional dependence: from 0.15 (standard deviation 0.08) for independent older people to 0.33 (0.08) for Day Hospital ($P < 0.05$) and 0.49 (0.08) for Continuing Care patients ($P < 0.005$).

Four patients declined venesection. Sufficient venous specimens were obtained to measure WBC count in 106 patients (96%), albumin in 91 (83%), CRP in 89 (81%), IL-6 in 106 (96%) and TNF-α in 105 subjects (95%). One patient had an extreme CRP value of 283 mg/l and one had a high lymphocyte count secondary to known chronic lymphocytic leukaemia. These cases were excluded, respectively, from further CRP and WBC analyses.

Table 2 shows the levels of each inflammatory marker across frailty definitions, as well as the variation of each marker within each frailty group. With increasing patient frailty as defined by function (independent/intermediate/dependent) and Fried phenotype (non-frail/pre-frail/frail), TNF-α and CRP each increased significantly. Both the presence of IL-6 and the levels in those in which it was detectable were higher in the frailer participants. Albumin was lowest in the frailest subjects by each definition. Table 3 shows estimates for the differences between groups defined by increasing levels of frailty, both univariate and adjusted for multiple covariates. The greatest differences were seen between intermediate and dependent groups and between the pre-frail and frail. Adjustment for multiple covariates (age, sex, BMI category, smoking status, number of co-morbidities and number of prescribed medications) did not account for any of the observed differences in levels of inflammatory markers; many differences were more marked after adjustment.

The Frailty Index correlated significantly with log-transformed CRP ($r = 0.221$, $P < 0.05$), log-transformed IL-6 ($r = 0.369$, $P < 0.01$) and TNF-α ($r = 0.379$, $P < 0.01$). There was a significant inverse correlation between Frailty Index and albumin

Table 1 Study subject characteristics

	Fried			Function		
	Non-frail	**Pre-frail**	**Frail**	**Independent**	**Intermediate**	**Dependent**
	$n = 22$	$n = 25$	$n = 63$	$n = 40$	$n = 40$	$n = 30$
% Men	55	44	33	40	40	40
		$P = 0.195$			$P = 1.000$	
Age, years * (S.D.)	79.7 (3.7)	85.2 (4.9)	84.8 (5.6)	82.7 (5.5)	84.2 (4.9)	84.9 (6.2)
		$P < 0.005$			$P = 0.215$	
Frailty Index*, † (S.D.)	0.10 (0.05)	0.22 (0.09)	0.41 (0.10)	0.15 (0.08)	0.33 (0.08)	0.49 (0.08)
		$P < 0.005$			$P < 0.005$	
Number of co-morbidities† (S.D.)	2.3 (1.9)	3.2 (1.8)	3.5 (1.6)	2.6 (1.5)	4.2 (1.6)	2.6 (1.3)
		$P = 0.018$			$P < 0.005$	
Prescribed medication (S.D.)*, †	2.9 (1.9)	5.6 (2.9)	5.3 (2.6)	4.0 (2.5)	6.3 (4.2)	4.3 (2.4)
		$P < 0.005$			$P < 0.005$	
Regular anti-inflammatory medication	9%	20%	13%	17.5%	12.5%	10%
		$P = 0.524$			$P = 0.624$	
Smoking current	0	0	5%	0	7.5%	0
Ex	50%	52%	37%	50%	50%	23.3%
None	50%	48%	33%	50%	42.5%	23.3%
Unknown	0	0	25%	0	0	53.3%
		$P = 0.536$			$P = 0.364$	
Obesity	9%	24%	5%	12.5%	15%	0
		$P = 0.025$			$P = 0.094$	

*Denotes significant differences between study groups defined by Fried frailty criteria.
†Denotes significant differences between study groups defined by function.

($r = -0.545$, $P < 0.01$) but no correlation with WBC count ($r = 0.176$, $P = 0.072$).

Discussion

In this study, we have shown significant associations between frailty and markers of inflammation. Although frailty is defined and measured in different ways, there is universal agreement that it is a state of increased vulnerability to a range of adverse outcome in later life, including death, institutionalization and worsening health [11, 13, 29–31]. We have applied three distinct measures of frailty: the 'phenotypic frailty' defined by Fried and colleagues, a Frailty Index and a measure of frailty defined by level of dependence. Our results were consistent, suggesting the association with inflammation does not depend on the specific definition or measure of frailty applied. Although older people in the 'dependent' group were disabled, and frailty is distinct from disability [32], we feel that they were also frail. There was strong face validity for choosing long-term inpatients as the 'frailest' group on the functional frailty spectrum. Construct validation of their frailty status is afforded by the higher prevalence of Fried frailty and significantly

Table 2 Inflammatory markers according to different frailty criteria

	Fried			Function		
	Non-frail	**Pre-frail**	**Frail**	**Independent**	**Intermediate**	**Dependent**
	$n = 22$	$n = 25$	$n = 63$	$n = 40$	$n = 40$	$n = 30$
White blood cell count $\times 10^9$/l mean (standard deviation)	6.7 (1.3)	7.1 (1.7)	7.7 (2.4)	7.1 (2.1)	7.3 (2.0)	7.8 (2.3)
		$P = 0.095$			$P = 0.450$	
Albumin g/l mean (standard deviation)	43.4 (5.3)	44.2 (3.5)	39.5 (5.6)	44.0 (4.5)	43.0 (3.4)	34.7 (4.7)
		$P < 0.005$			$P < 0.005$	
C-reactive protein mg/l median (25th and 75th percentile)	3.0 (2.0–5.0)	4.0 (2.0–6.0)	5.0 (3.0–13.0)	3.5 (2.0–5.5)	4.0 (2.0–11.0)	5.5 (2–21.5)
		*$P = 0.013$			*$P = 0.026$	
IL-6 pg/ml median (25th and 75th percentile)	0 (0–1.51)	0 (0–3.99)	3.59 (0.26–10.44)	0 (0–2.81)	1.48 (0–5.94)	6.97 (2.56–38.34)
		*$P = 0.068$			*$P < 0.005$	
% With detectable IL-6	41%	44%	80%	45%	67%	81%
		$P < 0.005$			$P = 0.011$	
TNF-α pg/ml mean (standard deviation)	1.50 (0.89)	1.86 (1.23)	3.19 (2.68)	1.68 (1.12)	2.01 (1.16)	4.58 (3.30)
		$P < 0.005$			$P < 0.005$	

*P = significance of differences in log-transformed values.

higher Frailty Index score in these patients. Our results were not affected by adjusting for age, sex, BMI, smoking, the number of medications being taken or number of co-morbidities.

The study has important limitations. Number of participants was small. The variables were not operationalized exactly as proposed by Fried and colleagues [8], although similar modifications have been made by others who have replicated the work [33]. Such adaptations are less of a problem for the Frailty Index approach, which does not require the same items or the same number of items to estimate the proportions that represent the Index's values [34]. In this study, a Frailty Index was constructed from 30 variables and though 40 are recommended [27], Frailty Indices have been constructed using as few as 20 variables [35].

As with other cross-sectional studies [9, 10], the association between frailty and inflammation provides no insights into causality. Inflammation may be part of the driving force towards disability. Increased levels of IL-6 have been linked to physical decline and disability [36, 37], and the development of age-related conditions such as dementia, Parkinson's disease, atherosclerosis and type 2 diabetes is associated with elevated levels of inflammatory mediators [38]. Furthermore, the association of inflammation with obesity, smoking and physical inactivity may constitute a link between life-style factors and frailty development [39].

Alternatively, inflammation may be a compensatory response. Some genotypes are associated with increased production of certain cytokines [40]. A direct link between such genotypes and frailty development or mortality would support a direct pathogenetic role of inflammatory mediators. To date, no such link has been established and the evidence regarding polymorphisms and longevity is conflicting [39]. One of the main functions of IL-6 is self-limiting inflammation [41]. Thus, elevated levels of IL-6 in frailty may be aimed at resolving an inflammatory response [42] initially triggered by viral antigens such as cytomegalovirus [43] or other sub-clinical disease such as asymptomatic bacteriuria [44].

Thirdly, inflammation may be an epi-phenomenon, merely a marker of the key causal mechanism. Excessive and unopposed oxidative stress may be the core mechanism leading to age-associated frailty [42]. Oxidative damage accumulates with age

Table 3 Differences in inflammatory markers between frailty groups, with 95% confidence intervals*

	Function					
	Intermediate *versus* independent			**Dependent *versus* intermediate**		
	Effect	**95% CI**	***P*-value**	**Effect**	**95% CI**	***P*-value**
Univariate						
White blood cell count	0.19	(−0.74, 1.13)	0.683	0.47	(−0.56, 1.50)	0.378
Albumin	−1.00	(−2.94, 0.94)	0.315	−8.31	(−10.53, −6.08)	$P < 0.005$
Log-transformed C-reactive protein	0.30	(−0.23, 0.83)	0.276	0.57	(−0.03, 1.16)	0.068
Log-transformed IL-6	0.25	(−0.58, 1.08)	0.563	1.78	(1.00, 2.57)	$P < 0.005$
Detectable IL-6†	2.44	(0.98, 6.09)	0.055	2.20	(0.68, 7.14)	0.189
TNF-α	0.32	(−0.52, 1.17)	0.454	2.57	(1.62, 3.52)	$P < 0.005$
Adjusted						
White blood cell count	−0.37	(−1.39, 0.66)	0.485	1.85	(0.50, 3.20)	0.009
Albumin	−1.23	(−3.41, 0.96)	0.276	−7.60	(−10.88, −4.33)	$P < 0.005$
Log-transformed C-reactive protein	0.42	(−0.14, 0.98)	0.143	1.07	(0.24, 1.90)	0.014
Log-transformed IL-6	0.17	(−0.85, 1.19)	0.746	2.70	(1.53, 3.86)	$P < 0.005$
Detectable IL-6†	1.76	(0.58, 0.54)	0.317	13.60	(1.35, 136.93)	0.027
TNF-α	0.43	(−0.39, 1.25)	0.310	3.50	(2.38, 4.62)	$P < 0.005$
	Fried					
	Pre-frail *versus* non-frail			**Frail *versus* pre-frail**		
	Effect	95% CI	*P*-value	Effect	95% CI	*P*-value
Univariate						
White blood cell count	0.47	(−0.73, 1.67)	0.443	0.61	(−0.37, 1.59)	0.225
Albumin	0.82	(−2.39, 4.02)	0.618	−4.71	(−7.33, −2.09)	$P < 0.005$
Log-transformed C-reactive protein	0.04	(−0.67, 0.74)	0.918	0.70	(0.13, 1.27)	0.019
Log-transformed IL-6	0.83	(−0.57, 2.23)	0.249	0.50	(−0.54, 1.55)	0.349
Detectable IL-6†	1.13	(0.36, 3.62)	0.831	4.50	(1.65, 12.26)	$P < 0.005$
TNF-α	0.37	(−0.85, 1.59)	0.556	1.33	(0.33, 2.32)	0.011
Adjusted						
White blood cell count	0.14	(−1.26, 1.54)	0.844	0.79	(−0.26, 1.85)	0.145
Albumin	0.36	(−3.14, 3.86)	0.841	−3.18	(−5.75, −0.60)	0.018
Log-transformed C-reactive protein	0.26	(−0.53, 1.04)	0.523	0.83	(0.24, 1.41)	0.007
Log-transformed IL-6	1.14	(−0.48, 2.77)	0.173	0.47	(−0.81,1.75)	0.473
Detectable IL-6†	1.00	(0.22, 4.53)	0.999	8.28	(2.29, 29.92)	$P < 0.005$
TNF-α	0.85	(−0.44, 2.14)	0.200	1.39	(0.41, 2.36)	0.007

*Both univariate differences and differences adjusted for age, sex, BMI, smoking, number of co-morbidities and number of prescribed medications are presented. Frailty is defined both by function (top) and by Fried frailty criteria (bottom).
†Reported effect size is the odds ratio of the presence of detectable levels of IL-6 between groups.

causing DNA, muscle and lipid damage sufficient to impair cellular and organ function [45]. Recent evidence supports a direct causal role for reactive oxygen species (ROS) in skeletal muscle damage. Protein carbonylation, an indirect measure of ROS muscle damage, was associated with low grip strength in the Women's Health and Ageing Study 1 [46].

This study provides further evidence linking inflammation and frailty in older people, an association that seems consistent across different frailty measures. Further studies are needed to establish the nature of this association – whether inflammation is primarily causal, compensatory or an epi-phenomenon. Intervention studies modulating the production or effect of inflammatory mediators are therefore a more distant prospect.

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