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Association between inflammatory markers and frailty in institutionalized older men

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ABSTRACT

Objectives: To determine whether higher serum levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and high sensitivity C-reactive protein (CRP) were associated with frailty in the older institutionalized men.
Participants: The study enrolled 386 residents from a veterans care home in northern Taiwan in 2007. All participants were men. Residents younger than 65 years or with acute illness were excluded.
Methods: Frailty status was determined based on the frailty phenotype (indicators include weight loss, exhaustion, and low grip strength, slow walking speed). Participants with 3 or more of the indicators were defined as frail, with 1 or 2 as intermediate frail, with no as non-frail. Serum IL-6, TNF-α, and hsCRP levels were measured using enzyme-linked immunosorbent assay and modeled as tertile for severely skewed distributions.
Results: The mean age of the participants was 81.5 ± 4.9 years. The percentages of frail were 33.2%, intermediate frail 59.1% and nonfrail 7.8%. Higher IL-6 level was positively associated with the frail status. Adjusting for age, body mass index, smoking status, and comorbid conditions, serum IL-6 showed significant trend across frailty categories ($P = 0.03$ [95% CI 1.40–5.24]). No significant associations of TNF-α, and CRP level with frailty were observed. An IL-6 level of 1.79 pg/mL had the optimal predictive value for frailty, with an area under the receiver operating characteristic (ROC) curve of 0.66 ($P = 0.01$ [95% CI 0.53–0.78]).
Conclusion: Higher serum levels of IL-6 were associated with frailty status in the older institutionalized men with multiple comorbidities.

1. Introduction

Frailty has been perceived as a major geriatric syndrome that leads to a higher risk of disability, falls, hospitalization, and mortality [1–3]. About 10–25% of people aged 65 years and above are found to be frail, with even higher percentage in people aged 85 years and above [4]. There is a growing consensus reporting that frailty is a state of decreased resistance to stressors and declined ability to maintain homeostasis that results from dysregulation across multiple biologic and physiologic systems in older people [2,3]. Chronic low-grade inflammation has been postulated to be an underlying mechanism of frailty. Researchers have indicated that increased levels of inflammatory markers, such as interleukins-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) were associated with decreased muscle strength, poor physical function, frailty, and mortality [5–9]. However, the target population of those studies was mainly the community-dwelling older people and some included only women.

Abbreviations: IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; hsCRP, high sensitivity C-reactive protein; ROC, receiver-operating characteristic; AUC, area under the curve.

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In this study, we aimed to evaluate whether inflammatory markers were related to different frailty stages in the older institutionalized people with multiple comorbidities. In addition, we intended to define the potential cut-off point of the biomarker levels to identify the presence of frailty in this group of people.

2. Materials and methods

2.1. Study population

In 2007, the residents of the Banciao Veterans Care Home, a long-term care facility in northern Taiwan build up for caring the veterans with disability or social need, were invited to participate in the study. All the residents in this long term care facility were men mostly retired and retrieved from Mainland China during World War II. Residents who were younger than 65 years, unable to communicate, and who do not consent, were excluded. We also excluded residents with acute medical problems because of the possibility of alterations in inflammatory markers during acute illness. This research protocols were approved by the Ethics Committee at Yang-Ming University, Taipei, Taiwan and written informed consent was obtained from all of the participants prior to inclusion of the study.

2.2. Frailty definition

The previously validated criteria of frailty reported by Fried et al. [2] included five components – weight loss, exhaustion, low grip strength, slow walking speed, and low levels of physical activity. The physical activity domain was not included in the study because of poor differentiability of this domain in these very old institutionalized participants who have sedentary lifestyle. Participants with three or more of the four indicators were defined as frail, one or two were defined as intermediate fail, and with no as nonfrial.

Unintentional weight loss of more than 10 pounds in the preceding year was assessed by reviewing annual health records in the veterans home. Exhaustion was evaluated by Center for Epidemiologic Studies Depression Scale (CES-D). Grip strength was measured on the dominant side with a digital hand grip dynamometer for three times (T.K.K. 5401, Takei Scientific Instruments Corporation, Japan). The highest record was taken as the maximal grip strength. Walk time was measured by timed 15-foot walk, stratified by height.

2.3. Biomarkers

Inflammatory biomarkers, IL-6, TNF-α, and hsCRP were measured in −80 °C frozen-stored blood samples, which were obtained in the morning after an overnight fasting. The serum levels of IL-6 and TNF-α were measured with Quantikine ELISA kits (R&D Systems, Minneapolis, MN). The hsCPR was measured with AssayMax ELISA kit (Assaypro, St. Charles, MO). The lower detection limits were 0.16 pg/mL for IL-6 ($n = 318$), 0.5 pg/mL for TNF-α ($n = 324$), and 0.25 ng/mL for hsCRP ($n = 383$).

2.4. Covariates

Smoking status was classified as either current or non-smoker. Data of concomitant use of oral anti-inflammatory drugs within 7 days (non-steroid anti-inflammatory drugs [NSAIDs], aspirin, and corticosteroids) and comorbidities was collected by one clinician by reviewing the medical records from the medical clinic within the institution and the main tertiary referral medical center. The comorbidities were categorized into diabetes mellitus, cardiovascular disease (including coronary heart disease, congestive heart failure, peripheral arterial disease, and cerebrovascular accident), chronic obstructive pulmonary disease, chronic renal failure, cancer, dementia, and depression.

2.5. Statistical analyses

Demographic characteristics in participants across different frailty stages were compared using χ^2 tests for categorical variables and one-way ANOVA for continuous variables. Spearman rank correlation was used to examine the associations among each biomarker in order to test the internal consistency of the biomarkers.

Because IL-6, TNF-α, and CRP were not normally distributed, they were categorized into tertiles with nearly equal numbers across each category. The lowest tertile of IL-6, TNF-α, and CRP was designated as the referent category. The top tertile was defined as “high inflammatory markers”. The association between frailty and each serum inflammatory marker was evaluated separately by ordinal logistic regression. The association between total counts of “high inflammatory markers” and frailty was also investigated.

Frailty was the dependent variable in the modeling process. In the unadjusted models, the frailty states were modeled as being frail compared to no or intermediate frail, and frail or intermediate frail to no frail. In model 1, association between frailty and each biomarker was evaluated after adjusted for age. In model 2, analyses additionally adjusted for smoking status, use of anti-inflammatory drugs, and comorbid conditions (diabetes mellitus, cardiovascular disease, COPD, chronic renal failure, cancer, dementia, and depression). The assumption of proportionality was met for each analysis. Trend tests were performed to evaluate whether there was a significant linear trend for biomarkers change across frailty stages. Participants with missing covariate data were included in the model using missing-indicator method [10].

Receiver-operating characteristic (ROC) curves were used to test the performance of the biomarkers to discriminate non-frail participants from frail participants. The optimal cut-off point to predict the presence of frailty was determined by Youden’s index. All analyses were performed with SPSS (version 18, SPSS Inc., Chicago, IL). A P value < 0.05 (two tailed) was considered as statistically significant.

3. Results

The study population included 386 men with a mean age of 81.5 ± 4.9 and a range from 67.0 to 100.4 years old. The median of IL-6, TNF-α, and CRP was 2.50 pg/mL (range 0.45–190), 1.20 pg/mL (range 0.13–28.2), and 1.83 ng/mL (range 0.01–16.0), respectively (Table 1). One hundred and twenty-eight persons (33.2%) were categorized as frail, 228 persons (59.1%) as intermediate frail, and 30 (7.8%) as nonfrail. Demographic characteristics for participants with different frailty status are shown in Table 2. There were significant differences in mean age and BMI among frailty groups. The post hoc test showed the age of frail and intermediate frail groups were older than non-frail group (82.4 year vs. 79.0 years, $P = 0.003$ and 81.6 year vs. 79.0 years, $P = 0.030$, respectively), and the BMI of frail group was significantly lower than intermediate frail group (23.0 kg/m^2 vs. 24.4 kg/m^2, $P = 0.003$). No differences were found in smoking status, anti-inflammatory drug use, and comorbidities.

The ordinal logistic regression revealed that higher IL-6 level was positively associated with frailty. In the unadjusted model, higher tertiles of serum IL-6 were positively associated with greater frailty states. In model 1, after adjusted for age, participants in middle and top tertiles of serum IL-6 were still more likely to be frail [odds ratio (OR) 2.12, 95% confidence interval (95% CI) 1.21–3.74; OR = 2.66, 95% CI 1.51–4.69]. In model 2, the associations persisted after further adjustment for BMI, smoking status, anti-inflammatory drug use, and comorbidities (OR = 2.28,

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