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Original Article

Monocytes Related Inflammatory Biomarkers are Associated With Frailty Syndrome

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SUMMARY

Background: Frailty is an age related syndrome that can lead to a higher risk of falls, disability, hospitalization, and mortality. Although the mechanism of the development of frailty remains unclear, chronic low-grade inflammation may explain part of it. Monocytes are one of the key components of innate immune response, and its over excitation may contribute to the development of frailty via chronic low-grade inflammation. Therefore, we investigated the associations between frailty and several monocytes related inflammatory biomarkers.

Methods: This study is a cross-sectional study conducted in Southwest China. Participants older than 60-year-old were included and sorted into frail, pre-frail, and non-frail groups. Concentrations of MCP-1, MCP-3, MIP-1α, MIP-1β and IL-10 were measured using enzyme-linked immunosorbent assay.

Results: Total enrolled participants were 306. There were 145 (47.4%) non-frail, 146 (47.7%) pre-fail, and 15 (4.9%) frail. Concentrations of MCP-1, MIP-1α and MIP-1β were significantly different among frail, pre-frail, and non-frail groups ($p = 0.009$, $p = 0.039$ and $p = 0.014$ respectively). After adjusting for several covariates, elevated concentrations of MCP-1 (>250.91 pg/ml) and MIP-1β (>211.41 pg/ml) in frail/pre-frail people remained significant compared with the non-frail (for MCP-1 $p = 0.03$, OR = 2.502, and for MIP-1β $p = 0.015$, OR = 2.602) while MIP-1α lost its significance. No significant associations were observed in IL-10 and MCP-3.

Conclusion: High concentrations of MCP-1 and MIP-1β were associated with frailty syndrome. Monocytes related cytokines may contribute to the development of frailty.

1. Introduction

Frailty is an age related syndrome marked with decline of physical reservation and higher vulnerability. Overall, 10.7% community dwelling people older than 65 are in frail status[1] which can lead to a higher risk of falls, disability, hospitalization, and mortality. The mechanism of the development of frailty remains unclear. In systemic level, immune and inflammatory responses, stress response, as well as neuroendocrine response may contribute to it[2]. Among all, chronic low-grade inflammation, marked with elevated level of cytokines, has been postulated to be one of the most important pathways[3]. It is widely accepted that our immune system has been stimulated by antigen continuously. Thus immune response in aged individuals may evolve in a persistent pro-inflammatory state accompanied by over production of free radicals and pro-inflammatory cytokines, which may induce a 'collateral damage' to host tissues and then contribute to frailty[4]. Previous studies have shown that inflammatory factors, such as interleukin (IL) -6 and C-reactive protein (CRP), are associated with frail status[5,6], which partially supported this hypothesis. Monocytes, being as one of the key components in the innate immune response and the first-line defensive cells, are more likely to be continuously activated and thus they may play a potential role in the pathogenesis of frailty. It has been found that monocyte counts are associated with frailty in disabled older women[7]. Cytokines related to monocytes, such as monocyte chemoattractant protein-1 (MCP-1), MCP-3, macrophage inflammatory protein-1α (MIP-1α), MIP-1β and interleukin-10 (IL-10), are reported to be associated

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with physical performance[8,9] or aging[10], and frailty is an age related syndrome marked with decline of physical performance. Thus we detected these cytokines to investigate their association with frailty.

2. Patients and methods

2.1. Study population

Study participants were from the Comprehensive Geriatric Assessment and Health Care Service Study, a cross-sectional study conducted in Southwest China. People older than 60-year-old were included as described previously[11], while participates who had acute infection diseases were excluded. Written informed consent was obtained and all questionnaires were conducted by fully trained interviewers. The study was approved by the Research Ethics Committee of Sichuan University.

2.2. Frailty definition

The identification of frailty was determined using a revised version based on the Fried frailty phenotype[12]. Shrinking was assessed by body mass index (BMI) below 18.5 kg/m^2[13,14]. Weakness, assessed by grip strength of the dominant hand, was measured twice with a digital handheld dynamometer (EH101; Xiangshan Inc., Guangdong, China). Exhaustion was identified using individual items obtained from the Geriatric Depression Scale (GDS)[15]. Slowness, assessed by walking time, was measured twice using a 20-m walking distance. Average measure of grip strength or walking time lower than the 20th sex-specific percentile was defined as decreased. Low activity, assessed by physical activity questionnaire, was defined as performed light-intensity physical activities or inactive[16]. Over all, participants with 3 or more components were considered as frail, 1 or 2 as pre-frail, and 0 as non-frail.

2.3. Blood sampling and assessment of cytokines

Fasting venous blood samples were obtained and centrifuged at 300rcf for 20 min at room temperature to isolate serum, which were then frozen and stored at −80 °C until the enzyme-linked immunosorbent assay (ELISA) was performed. MCP-1, MCP-3, MIP-1α, MIP-1β and IL-10 were quantified with ELISA (Human Cytokine/Chemokine ELISA set; Beijing FreeMore Biotechnology Co, Ltd.).

2.4. Covariates

Demographic data were collected using a general questionnaire. Comorbidities such as hypertension, coronary heart disease, chronic obstructive pulmonary disease (COPD) and diabetes mellitus were verified by reviewing the medical records. Physical performance was assessed using Short Physical Performance Battery (SPPB)[17]. Cognitive performance was assessed using Mini−Mental State Examination (MMSE)[18]. Dependence was assessed using Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL). Depression was assessed using GDS. BMI was calculated as $\frac{body\ weight(kg)}{hight^2(m^2)}$.

2.5. Statistical analysis

Data analysis was performed using IBM SPSS 20.0 package (SPSS Inc., Chicago, IL), and the statistical significance was set at $p < 0.05$. Continuous variables were presented as mean ± standard deviation (SD), and frequencies for categorical variables. Differences of continuous variables among groups were assessed using ANOVA for normal distribution and Kruskal−Wallis *U* test for non-normal distribution. Chi-square test was used for categorical variables, whereas the Fisher's exact test was used when over 1 cells have expected count less than 5 in Chi-square test. Multivariate-adjusted logistic regression models were used to estimate odds ratio (OR) and 95% confidence interval (CI).

3. Results

3.1. Characteristics of study participants

There were 306 participates enrolled, including 122 males (39.9%) and 184 females (60.1%), with mean age of 70.5 ± 6.6 years old. Of all, 145 (47.4%) people were categorized as non-frail, 146 (47.7%) as pre-fail and 15 (4.9%) as frail. Detailed demographic and clinical characteristics of this population were presented in Table 1. As illustrated, men and women were equal likely to be frail. Moreover, as we expected, frail status was associated with older age (76.1 ± 7.1 vs 69.6 ± 5.9, $p = 0.001$), lower educational level ($p = 0.007$), rural area living ($p < 0.001$), poorer physical function (SPPB score: 4.4 ± 0.7 vs. 4.9 ± 0.4, $p = 0.002$), poorer cognitive function (MMSE score: 20 ± 7 vs. 27 ± 4, $p = 0.001$), higher degree of dependence (ADL score: 8 ± 2 vs. 7 ± 0, $p < 0.001$; IADL score: 10 ± 4 vs. 7 ± 1, $p < 0.001$), as well as higher level of disability ($p < 0.001$). Higher proportion of depression assessed by GDS was also reported in frail people (score of 17 ± 6 vs. 5 ± 4, $p < 0.001$) compared with non-frail people. However, no significant differences were found in comorbidities, BMI, hematological parameters, smoking, and alcohol consumption.

3.2. Association between frailty and serum inflammatory factors

The average concentration was 199.80 pg/ml of MCP-1, 186.48 pg/ml of MCP-3, 75.51 pg/ml of MIP-1α, 166.04 pg/ml of MIP-1β and 22.85 pg/ml of IL-10. Among all five inflammatory factors, MCP-1 ($p = 0.009$), MIP-1α ($p = 0.039$) and MIP-1β ($p = 0.014$) showed significant differences among groups, while no differences were found in MCP-3 ($p = 0.340$) and IL-10 ($p = 0.327$), as shown in Table 1. People with higher concentrations of MCP-1, MIP-1α and MIP-1β were more likely to live in rural area, have lower education level and poorer cognitive function. Detailed comparisons between normal and elevated concentration (defined as elevated if the concentration exceeded the 75th percentile) of MCP-1 (>250.91 pg/ml) and MIP-1β (>211.41 pg/ml) were showed in Table 2.

To further substantiate the association between MCP-1, MIP-1α, MIP-1β and frailty, we combined pre-frail group and frail group to performed multivariate-adjusted logistic regression, due to small number of frail people (n = 15). Concentrations of inflammatory factors were divided as bottom (<25th percentile), middle (25th−75th percentile), and top (>75th percentile). After combination, only MCP-1 ($p = 0.003$) and MIP-1β ($p = 0.004$) were significantly associated with frail status (Fig. 1). Furthermore, this association was confirmed in different models that included adjustments for age, gender, BMI, smoking and drinking, comorbidities, functional abilities, depression, and cognitive function (Table 3).

4. Discussion

The present study found that higher concentrations of MCP-1 and MIP-1β were associated with frailty after adjusted for several covariates. It supported the hypothesis that chronic low-grade inflammation contributed to the development of frailty[3], and

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