

## Frailty and Potential Biomarkers in Aging

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### Abstract

Frailty is an age-related syndrome that has been well-described in the last ten years. It can be characterized by diminished strength, endurance, and reduced physiologic function. With multiple causes and contributors, frailty is highly correlated with functional decline and chronic diseases. Currently, there are no standardized tests or biomarkers that can be used to identify frail patients, though there have been a number of assessments used in research such as the Fried Frailty Phenotype or the Rockwood Frailty Index. Identification of biomarkers for frailty is a major consideration for future studies of this syndrome.

**Keywords:** Frailty; Biomarkers; Aging; Muscle mass

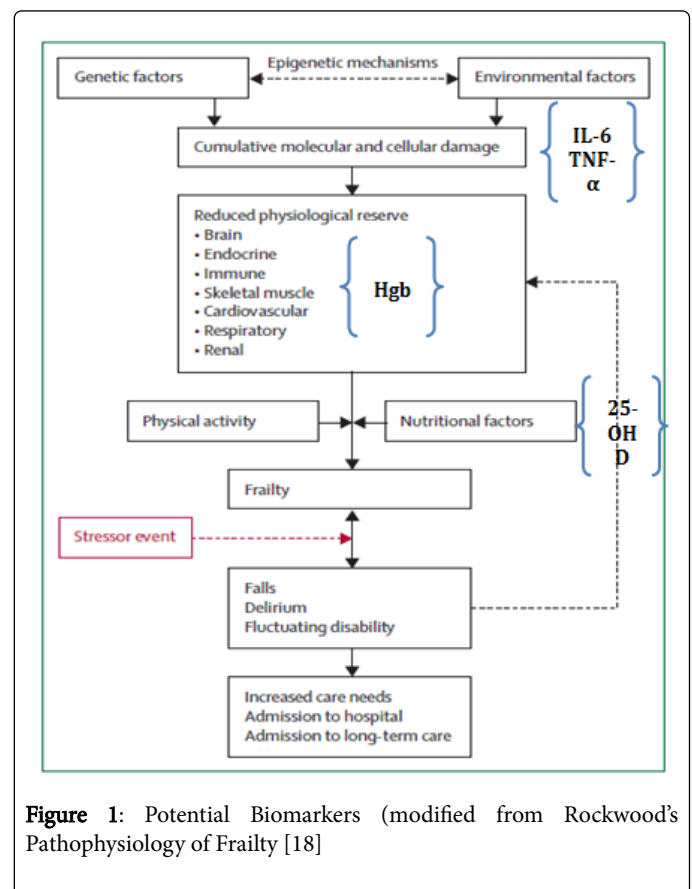
### Introduction

Frailty is an age-related syndrome that is highly correlated with functional decline and chronic disease, leading to loss of independence and increased mortality [1,2]. There are multiple causes and contributors to frailty, which can be characterized by diminished strength, endurance, and reduced physiologic function [3]. Theoretically, frailty has also been defined as a state of increased vulnerability due to aging-associated decline in reserve and function across multiple physiologic systems, leading to an inability to cope with chronic or acute stressors [4].

Although a number of biomarkers have been tested in relation to frailty, experts have agreed that no single biomarker by itself is adequate for the assessment of frailty [5]. There are some indications that a combination of biomarkers may be more useful, however there has been no consensus on which combination would be best. Therefore for clinical purposes, laboratory testing for frailty is not indicated. For research purposes, however, there are some more common biomarkers that have been shown to be associated with physical frailty [6,7].

### Inflammatory Markers

Interleukin-6 (IL-6) is a pro-inflammatory cytokine that has been studied as part of the theory that chronic inflammation leads to physical function decline and thereby increases frailty (Figure 1). One study in older adults has shown a significant association between elevated IL-6 blood concentrations and frailty as defined by the Fried Frailty Phenotype (low grip strength, slow walking speed, exhaustion, decreased physical activity, and weight loss) [8]. In addition, significant correlations have been found between high serum IL-6 levels and other physical measures such as decreased hand grip strength [9-11], decreased muscle mass [11], decreased lower extremity strength [11], slower gait speed [12], and difficulty walking or climbing steps [13].



**Figure 1:** Potential Biomarkers (modified from Rockwood's Pathophysiology of Frailty [18])

Elevations in another common inflammatory cytokine, tumor necrosis factor-alpha (TNF-α), has been associated with decreased hand grip strength [11], decreased muscle mass [11], decreased lower extremity strength [11], and difficulty walking or climbing steps [12].

C-reactive protein (CRP) is an acute phase reactant that is released by the liver during inflammation. High levels of CRP have been significantly associated with decreased hand grip strength [9,10], and difficulty walking or climbing steps [13]. In a large group of community-dwelling older adults, a cross-sectional analysis showed that phenotypically frail participants had increased levels of CRP [14].

### Clinical Markers

Since inflammatory markers are not commonly used in clinical practice, other markers such as hemoglobin have been studied to determine if they can be used for clinical diagnosis of frailty. Anemia

as defined by a hemoglobin (Hgb) concentration below 12 g/dL in women and below 13 g/dL in men was associated with disability in basic and instrumental activities of daily living, poorer performance on the Short Physical Performance Battery (walking, balance, standing), decreased lower extremity strength and decreased hand grip strength [15].

### Nutritional Markers

There has also been research into whether using nutrition or exercise can help reverse the effects of frailty. Vitamin D insufficiency is common in older adults and low levels of 25-hydroxyvitamin-D (25-OHD) have been associated with decreased gait speed, poor balance, more difficulty standing, and decreased lower extremity strength [16]. A study of older adult participants in the National Health and Nutrition Examination survey found inverse associations between frailty and blood 25-OHD levels [17].

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