Research Progress on the Correlation Between Multi-Dimensional Serum Biomarkers and Frailty in the Elderly

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Abstract: With the accelerated aging process in China, frailty has become an important geriatric syndrome that threatens the health of the elderly. Frailty is characterized by decreased physiological reserve and increased physical vulnerability, often leads to adverse health outcomes. Recently, serum factors have received widespread attention as potential biomarkers for early identification and risk assessment of frailty. In terms of chronic inflammation, levels of interleukin-6 (IL-6), C-reactive protein (CRP), and procalcitonin (PCT) are significantly elevated in frail individuals, showing a positive correlation with frailty phenotype; homocysteine (Hcy), as a metabolism-related factor, is closely associated with cognitive frailty; 25-hydroxyvitamin D (25(OH)D) and Klotho protein exhibit a protective effect against frailty, and their decreased levels are associated with an increased risk of frailty. Predictive models based on multi-markers have higher diagnostic performance than single markers, and proteomic studies also show the revealed protein signature associated with frailty. However, currently there is a lack of standardized serum factor's evaluation Protocol. This review provides a scientific basis for early clinical identification and intervention of frailty and the future research directions need focusing on the optimization and application validation of multi-marker combined models.

Keywords: Frailty; Serum Factor; Biomarker; Chronic Disease; Predictive Model

1. Introduction

According to the latest data from the National Bureau of Statistics, by the end of 2025, Chinese population aged 60 and above reached 323.38 million, with 223.65 million aged 65 and above, accounting for 15.9% of the total population. This represents an increase of 13.07 million and 3.42 million, respectively, compared to the previous year [1]. As the aging process accelerates, health concerns among the elderly population are becoming increasingly prominent, with frailty recognized as a significant threat to elderly health [2]. Frailty is a non-specific condition characterized by a decline in physiological reserve, increased vulnerability, and reduced resilience to stress, all associated with aging. It is a key geriatric syndrome, primarily manifested by decreased strength, endurance, and physiological function. Even minor stressors can trigger adverse events such as falls, hospitalization, disability, and even death. The onset of frailty results from a complex interplay of biological, psychological, and social factors, with physiological factors serving as the core foundation. These include multi-system functional decline, chronic inflammation, neuroendocrine imbalances, abnormal energy metabolism, comorbidities, malnutrition, and polypharmacy [3]. Depression and cognitive decline are significant risk factors for the onset and worsening of frailty, while social and environmental factors [4], lifestyle choices, genetic background, demographic characteristics, and educational attainment also exert a considerable influence. In China, the prevalence of frailty is 12.8% among community-dwelling elderly, 22.6% among hospitalized elderly, and 44.3% among elderly residents in nursing homes. Frailty has severely impacted the quality of life and health status of the elderly population, underscoring the growing importance of preventing and intervening in its onset and progression.

Assessment tools for frailty are mainly applied in clinical settings in the form of scales,

featuring a wide variety of forms, assessment dimensions, and pathways. These tools are primarily divided into two categories: those based on frailty phenotypes and those based on the accumulation of health deficits. Popular tools include the Fried frailty phenotype, frailty index, FRAIL scale, Edmonton frailty scale, and the F1 scale for research purposes [5]. Additionally, the significance of wearable devices, imaging biomarkers, and laboratory biomarkers in frailty assessment is becoming increasingly evident. Serum factors such as interleukin-6 (IL-6), C-reactive protein (CRP), tumor necrosis factor-α (TNF-α) [6], procalcitonin (PCT), 25-hydroxyvitamin D (25(OH)D), homocysteine (Hcy), and Klotho protein not only participate in the body's immune response, inflammatory processes, and metabolic regulation but also, to some extent, reflect an individual's health status and prognosis, playing a crucial role in the onset and progression of frailty. However, there are still considerable debates regarding the precise mechanisms by which these serum factors influence frailty, as well as the validity and reliability of these factors as biomarkers. This review aims to systematically review relevant literature, explore the potential value of various serum factors in diagnosing and predicting frailty, provide a scientific basis for early clinical identification and intervention, and outline future research directions.

2. Chronic Inflammation and Frailty

There exists a strong correlation between frailty and inflammatory factors. Frail patients frequently present with a chronic low-grade inflammatory condition, marked by elevated levels of inflammatory markers in peripheral blood, such as IL-6, CRP, and TNF-α [7]. With age increase, the levels of pro-inflammatory factors in their bodies gradually and slightly increase. This persistent low-grade inflammation can directly promote to muscle protein degradation, mitochondrial dysfunction, and/or neuroendocrine imbalances, subsequently leading to sarcopenia, reduced physical strength, and metabolic disturbances. Imbalances in inflammatory factor levels can impair the function of multiple systems, manifesting as frailty phenotypes including weight loss, fatigue, and a slower walking pace. Consequently, inflammatory factors not only serve as significant drivers in the onset of frailty but also act as potential biomarkers for evaluating frailty risk and the efficacy of interventions. Anti-inflammatory therapies may offer novel strategies for delaying the progression of frailty.

2.1 Interleukin-6 (IL-6)

The biological function of IL-6 in geriatric frailty has been extensively studied. Multiple studies have shown that the serum IL-6 levels in frail elderly patients are significantly higher than those in non-frail individuals [8], indicating a positive correlation between IL-6 and frailty. Patients with chronic diseases in stable phase, diabetes, hypertension, coronary heart disease, chronic heart failure, Diabetes with myopenia, serum IL-6 levels are closely related to geriatric frailty. Furthermore, elevated IL-6 is also an independent risk factor for coronary heart disease. The potential of IL-6 as a biomarker for monitoring frailty has been widely validated across different disease contexts.

2.2 C-Reactive Protein (CRP)

CRP is an acute-phase protein, expressed by hepatocytes, smooth muscle cells, and macrophages, regulated by IL-1, IL-6, and TNF-α. Since CRP monomers are present in cell membranes rather than in serum, conventional detection methods face challenges. High-sensitivity assays can be employed to detect high-sensitivity C-reactive protein (hs-CRP). As a non-specific inflammatory marker, CRP is implicated in inflammation and cardiovascular diseases such as atherosclerosis, serving as a robust predictor of cardiovascular events. It also plays a pivotal role in autoimmune diseases [9]. A longitudinal aging study conducted in the UK revealed that individuals with elevated levels of hs-CRP and white blood cells are at a higher risk of developing frailty [10]. The Korean National Health and Nutrition Examination Survey also confirmed, that age-related systemic low-grade inflammation significantly influences frailty, thereby supporting the potential of hs-CRP as a biomarker for frailty detection [11]. In elderly hypertensive patients, IL-33（Interleukin-33）, sST2（Soluble Suppression of Tumorigenicity 2）, CXCL10（C-X-C Motif Chemokine Ligand 10）, CCL2（C-C Motif Chemokine Ligand 2）, IL-6, and CRP are closely associated with frailty, and the combined detection of these six markers offers enhanced diagnostic value.

2.3 Procalcitonin (PCT)

PCT is a protein that increases markedly during bacterial infections and systemic inflammatory responses, and it is widely utilized for evaluating infection severity and guiding antibiotic therapy. Elevated PCT levels may indicate an intensified inflammatory state in elder, closely associated with the onset and progression of frailty.

Alterations in these inflammatory factors frequently coincide with the occurrence of other diseases. Combined monitoring aids in assessing the degree of frailty progression and offers objective evidence for evaluating the efficacy of personalized intervention strategies, assessing perioperative infections, and tracking the rehabilitation process.

3. Metabolic Factors Associated with Cognitive Decline

Cognitive impairment serves as a pivotal factor in the progression of frailty and in constraining the quality of life and disease prognosis of elderly individuals with chronic conditions. Thus, conducting an objective assessment of cognitive impairment holds substantial significance.

Homocysteine (Hcy) represents an intermediate metabolite in the sulfur-containing amino acid metabolic pathway, primarily influencing the functions of endothelial and smooth muscle cells. It plays a role in altering the structural integrity of the vascular wall and modulating the coagulation system, and is implicated in cardiovascular diseases, stroke, venous thromboembolism, recurrent miscarriages, neural tube defects, and Alzheimer's disease. Among elderly patients with H-type hypertension and cerebrovascular diseases, serum Hcy levels exhibit a significant positive correlation with cognitive frailty. The integration of blood pressure variability (BPV) measurements can facilitate early frailty screening [12], while the combination of CRP, IL-6, TNF-α, MMP-3, and oxidative stress markers such as MDA and SOD can aid in the objective evaluation of the severity of cognitive impairment in frail patients. Serum Hcy levels may potentially serve as a biomarker for cognitive decline [13].

4. Protective Factors against Frailty

4.1 25-hydroxyvitamin D (25(OH)D)

25(OH)D represents the activated form of vitamin D within the body, serving as an indicator of the body's vitamin D reserves. 1,25-dihydroxyvitamin D3 facilitates the absorption of calcium and phosphorus in the small intestine, influences calcium metabolism in bone tissue, maintains the equilibrium of calcium and phosphorus in the blood, and promotes the calcification of bones and teeth. Research indicates that in individuals with pre-frailty and frailty, symptoms such as impaired balance, increased risk of falls, urinary incontinence, depression, and hearing loss exhibit a negative correlation with serum 25(OH)D levels [14]. Among patients with elderly coronary heart disease, elderly type 2 diabetes mellitus complicated by sarcopenia, and early postmenopausal osteoporosis, those in the frail group demonstrate significantly lower serum 25(OH)D levels compared to their non-frail counterparts. Community-based screenings of elderly populations reveal a strong correlation between 25(OH)D and common comorbidities of frailty, including sarcopenia and dysphagia. Vitamin D plays a crucial role in calcium and phosphorus metabolism in both bone and muscle tissues, sustaining normal physiological functions. It also mitigates muscle breakdown by positively modulating mitochondrial function, thereby offering protective effects against sarcopenia and osteoporosis. Consequently, it holds potential as a significant biomarker for evaluating and preventing frailty in the elderly.

4.2 Klotho Protein

The Klotho protein has emerged as a focal point in research and therapeutic development for various diseases, owing to its potential in anti-aging, neuroprotection, renal protection, and metabolic regulation. A 2023 study published in *Nature Aging* revealed that the Klotho protein can stimulate neurogenesis in brain regions such as the hippocampus by activating platelets to release platelet factors, reverse alterations in the expression of aging-related cognitive genes and enhance cognitive function in both young and aged mice [15]. Clinical research indicates that Klotho protein levels decline with age and exhibit a negative correlation with frailty; higher Klotho levels are associated with a reduced risk of frailty [16]. In elderly patients with coronary heart disease complicated by frailty, serum levels of CC16 and Klotho are notably decreased, whereas levels of NF-kB, TNF-α, and IL-6 are significantly elevated.

The loss of motor neurons during the frailty phase can result in denervation and atrophy of muscle fibers, an imbalance between protein synthesis and breakdown, and a further acceleration of muscle wasting due to chronic inflammation. This manifests as a slower walking pace, weakness, fatigue, and a decline in grip strength. Resistance training can stimulate nerves and enhance muscle protein synthesis. Serum albumin, CRP, and 25(OH)D3 exhibit a negative correlation with frailty indicators. The antioxidant factor SOD plays a significant role in protecting the nervous system and alleviating cognitive impairment in frail patients.

Although Klotho protein and 25(OH)D are distinct biomarkers, their mechanisms of action in frailty may share similarities. Both demonstrate a protective effect against frailty at elevated concentrations, indicating their potential importance in preventing and reducing frailty in the elderly. Future studies should delve deeper into their specific mechanisms and clinical applications.

Other studies have shown that serum cystatin C, insulin-like growth factor-1 (IGF-1), and insulin-like growth factor binding protein-3 (IGFBP-3) are associated with frailty in the elderly. Qin Li et al. [17] analyzed the correlation between community-dwelling frailty and serum factors and found that hemoglobin, IGF-1, follicle-stimulating hormone, estradiol, and other factors were not significantly associated with frailty. Elevated serum growth differentiation factor-15 (GDF-15) is an independent risk factor for ICU-acquired weakness (ICU-AW) in patients with sepsis undergoing mechanical ventilation and has high predictive value. In summary, serum biomarkers play an important diagnostic role in frailty assessment, and the combined detection of multiple biomarkers can improve prediction accuracy, providing a scientific basis for early identification and intervention of frailty in clinical practice.

5. Prediction Model Based on Serum Factors for Decline

The frailty prediction model based on serum factors has emerged as a research hotspot recently, aiming to achieve early identification and risk stratification of frailty. Current research has evolved from single marker models to multi-marker combination models. IL-6 and high-sensitivity C-reactive protein (hs-CRP) have been confirmed to have the most stable positive correlation with frailty [18], while 25-hydroxyvitamin D (25(OH)D), Klotho protein, hemoglobin, and albumin exhibit stable negative correlations. Breakthroughs in proteomics research are reflected in the identification of frailty-related protein characteristics. prospective study has established a "proteomics frailty index" comprising 25 proteins and validated its predictive performance in different groups [19]. Latest research trends to integrate multiple serum factors into traditional frailty indices. A study from Hong Kong found that incorporating homocysteine (Hcy), hs-CRP, creatinine, and vitamin D into the frailty index significantly improved its predictive ability for cognitive impairment [20]. Despite the rapid progress of frailty, Lack of uniformity and standardization for serum factors, which is a direction for future breakthroughs.

6. Conclusion

This review focuses on the association between multidimensional serum biomarkers and frailty in the elderly, clarifying the distinct roles of various serum factors in the onset and progression of geriatric frailty. Chronic inflammatory factors including IL-6, CRP and PCT are significantly elevated in frail populations and serve as key drivers of frailty development. The metabolic factor homocysteine (Hcy) is closely associated with cognitive frailty and can act as a potential biomarker for cognitive decline. 25-hydroxyvitamin D (25(OH)D) and Klotho protein are protective factors against frailty, with decreased levels increasing frailty risk. Predictive models based on the combined detection of multiple biomarkers exhibit markedly higher diagnostic efficacy than single biomarkers. Proteomics has also provided new insights into identifying frailty-related protein signature profiles, and certain frailty indices integrated with serum factors have improved the ability to predict cognitive impairment. At present, relevant research still lacks standardized protocols for the assessment and prediction of serum factors, and the underlying associations of the mechanisms of action of various biomarkers have not been fully elucidated. Future research should focus on the optimization and clinical application verification of combined multi-biomarker models, further explore the

interactions between biomarkers, and establish unified detection and assessment standards. This will provide more precise scientific support for the early identification, risk stratification and personalized intervention of geriatric frailty, and facilitate the health management of the elderly population against the backdrop of aging.

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