Advances in Multi-omics-based Biomarker Research in Frail Elderly Populations: Postprint

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Abstract

Frailty in older adults refers to a non-specific state characterized by impairment of the homeostatic network system composed of multiple body systems, with sarcopenia as its fundamental feature, leading to decreased physiological reserve, reduced resistance to stressors, and diminished recovery capacity following stress. Early diagnosis of frailty is of significant value in helping older individuals restore health. In recent years, technological advances in omics research have provided new avenues for discovering potential specific, stable, and reliable biomarkers associated with early frailty. This article, after collating and analyzing relevant studies, reviews the research progress on blood-based frailty biomarkers from the perspectives of genomics, transcriptomics, proteomics, and metabolomics, which may facilitate frailty risk assessment, exploration of underlying mechanisms, development of targeted interventions, and promotion of healthy aging.

Full Text

Advances in Studies on Multi-omics-based Biomarkers of Frailty in the Elderly

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Abstract

Frailty in the elderly is a non-specific state characterized by systemic dysregulation across multiple physiological systems, with sarcopenia as its core manifestation, leading to diminished physiological reserve, reduced resilience to stressors, and impaired recovery capacity. Early diagnosis of frailty holds significant value for promoting health recovery in older adults. Recent technological advances in omics research have opened new avenues for discovering potentially specific, stable, and reliable biomarkers associated with early-stage frailty. Through comprehensive literature analysis, this review examines progress in frailty biomarker research from genomic, transcriptomic, proteomic, and metabolomic perspectives, focusing on blood-based markers. These findings may facilitate frailty risk assessment, elucidate underlying pathophysiological mechanisms, and inform targeted interventions to support healthy aging.

Keywords: Frailty; Pre-frailty; Multi-omics; Biomarkers

According to 2020 statistics, the global prevalence of frailty and pre-frailty among individuals aged 60 and above is 16% and 45%, respectively, imposing a substantial socioeconomic burden. Frailty is a multidimensional geriatric syndrome resulting from age-dependent decline in systemic regulatory functions, encompassing cumulative damage across multiple systems including muscle strength deterioration, age-related hormonal disturbances, inflammation, and nutritional or metabolic deficits. This condition leads to reduced physiological reserve capacity in physical activity, energy metabolism, cognition, and balance. Frailty not only increases risks of falls, disability, delirium, hospitalization, and mortality but also poses a major threat to health status and life expectancy in older adults. Some scholars propose that frailty may represent the clinical manifestation of subclinical stages of chronic diseases in the elderly. Consequently, early diagnosis is crucial for minimizing frailty progression (primary prevention), mitigating or delaying potential chronic diseases and symptoms (secondary prevention), and controlling adverse clinical outcomes such as recurrent hospitalization and mortality (tertiary prevention).

The development of frailty involves multiple complex and aberrant physiological processes, including chronic inflammatory responses, energy imbalance, oxidative stress, endocrine dysregulation, sarcopenia, and malnutrition, which complicate effective clinical diagnosis and intervention. The phenotypic heterogeneity and complexity of multisystem dysregulation in individuals make comprehensive assessment challenging and render biomarker discovery for frailty particularly difficult. Numerous studies have sought omics-based biomarkers to evaluate frailty risk and its consequences, yet a systematic synthesis is lacking. Therefore, this review synthesizes extensive literature and research findings to describe advances in frailty biomarkers from epigenomic, transcriptomic, proteomic, and metabolomic perspectives, providing insights for clinical practice and research in geriatric frailty.

1.1 Single Nucleotide Polymorphism (SNP)

Genetic regulation of differential gene expression plays an important role in explaining inter-individual variation in frailty development. Research indicates that due to genetic variation, circulating cytokine concentrations differ among frail individuals even under identical inflammatory conditions, with genetic variants present in genes involved in frailty-related pathways such as inflammatory response, immune regulation, muscle function decline, apoptosis, autophagy, and lipoprotein regulation. Moreover, SNPs can significantly influence patient tolerance and adherence to exercise interventions, thereby affecting treatment outcomes. In summary, SNPs facilitate early identification of individuals at risk for frailty and investigation of potential pathogenic mechanisms, while also modulating responses to therapeutic interventions and influencing treatment efficacy. Studying the association between SNPs and frailty phenotypes thus holds considerable clinical potential.

1.2 Epigenetic Modifications

Epigenetic changes affect physiological processes across all cells and tissues throughout the lifespan, representing valuable predictive biomarkers for frailty. DNA methylation patterns undergo age-related remodeling and serve as mediators through which genetic and environmental factors influence frailty development, representing a primary focus in epigenetic research on frailty and related diseases. Studies have demonstrated that frailty progression is associated with significant global DNA methylation reduction and promoter-specific CpG site hypermethylation. Epigenetic clocks developed based on DNA methylation levels, such as "GrimAge" and "DNAm-PhenoAge," show strong predictive capacity for frailty and mortality. DNA methylation thus links epigenetics with health changes to become an indicator for predicting frailty development. However, application of epigenetic clocks for frailty prediction requires larger-scale data across diverse populations, ethnicities, sexes, tissues, cells, and disease states to minimize prediction errors.

2.1 MicroRNA (miRNA)

As evolutionarily conserved non-protein-coding RNA molecules, miRNAs regulate multiple processes including intercellular communication, differentiation, and proliferation, and mediate mechanisms central to frailty development such as inflammaging, muscle atrophy, and mitochondrial damage. Aging and frailty are characterized by elevated oxidative stress and inflammation, marked by increased miRNA expression (Table 1). Iryna et al. confirmed significant elevation of three inflammation-related miRNAs (miR-21, miR-146a, and miR-223) in blood samples from frail individuals, while expression of miR-483 and miR-223 associated with melatonin synthesis—possessing anti-aging properties—was reduced. Furthermore, numerous miRNAs are implicated in muscle atrophy and undergo significant changes following acute and/or sustained exercise, suggesting important roles in both pathological and physiological muscle processes.

Since early intervention can modulate miRNA expression to influence gene expression, miRNAs represent potential therapeutic targets for frailty to alleviate muscle homeostasis imbalance and maintain mitochondrial function.

2.1 Peripheral Blood Mononuclear Cell Total RNA

Calais S Prince et al. performed sequencing of total RNA from peripheral blood mononuclear cells and identified eight genes whose expression was affected by frailty, including SLC2, SLC2A6, FCGR3B, TEPSIN, C17orf56, OSM, CXCL1, IL6, IL1B, and EGR1. Notably, EGR1 expression showed significant interaction with frailty, while SLC2A6, FCGR3B, and C17orf56 expression levels were significantly negatively correlated with frailty severity. Youwen Zhang et al. conducted coordinate analysis of total RNA levels from peripheral blood mononuclear cells in the GEO public database, revealing that differences between frail and non-frail groups involved cellular metabolic regulation and macromolecular metabolic processes, with TSIX, BEST1, and ADAMTSL4 identified as genes warranting further investigation.

3 Frailty Proteomic Biomarkers

Proteomics aims to link genes with phenotypes by investigating protein expression, regulation, interactions, and function to rapidly identify global protein alterations in cells, tissues, or organisms. Proteomic studies indicate that frailty-associated dysregulation involves pathways including inflammation, apoptosis, calcium homeostasis, neuronal signaling (central and peripheral nervous systems), hormonal regulation, and gene expression/transcriptional control. Muscle proteins, chronic low-grade inflammation, and characteristic vascular and blood proteomic profiles may aid in diagnosing or predicting frailty.

3.1 Muscle Mass and Strength

Age-related decline in muscle function and weakness (sarcopenia) represents the primary cause of mobility loss and frailty in older adults and constitutes a core frailty marker. Staunton et al. reported age-dependent alterations in 19 proteins in the vastus lateralis muscle involved in excitation-contraction-relaxation cycling, muscle metabolism, ion handling, and cellular stress responses. Carbonic anhydrase 3 (CA3) isoforms showed increased abundance during muscle aging, suggesting CA3 as a potential sarcopenia biomarker. Ceereena et al. found insufficient energy metabolism-related proteins but excessive proteins associated with innate and adaptive immunity, proteostasis, and alternative splicing in older adults' muscles, likely related to energy metabolism disruption, pro-inflammatory environment, and increased proteolysis.

3.2 Inflammatory Proteins

Chronic inflammation is consistently associated with frailty in biomarker research. Senescent cells secrete pro-inflammatory factors that may contribute to chronic inflammation and frailty. Some pro-inflammatory cytokines are hypothesized to exert catabolic effects on muscle, and low-grade inflammatory states may exacerbate common clinical symptoms in older adults, particularly sarcopenia and cachexia. Studies in frail subjects demonstrate that elevated interleukin-6 (IL-6), IL-1, tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) are associated with increased morbidity and mortality in older adults, with TNF-α and IL-6 specifically proposed as frailty markers. While IL-6 and CRP have been investigated as potential biomarkers in clinical trials, their utility for early identification, risk stratification, and prevention has proven limited. Moreover, these inflammatory markers are non-specific, increasing under various inflammatory, neoplastic, or infectious conditions, which restricts their application for frailty screening.

3.3 Vascular System Proteins

Serum is a complex biological fluid containing proteins spanning at least nine orders of magnitude in concentration. Proteomics can analyze complex plasma protein level changes, offering important insights into protein dysfunction or altered expression. J Chew et al. identified serum myostatin in men and insulin-like growth factor 1 (IGF-1) in women as potential biomarkers for concurrent sarcopenia and frailty in community-dwelling older adults. Lin et al. found that angiotensinogen (AGT), kininogen-1 (KG), and antithrombin III (AT) increased with frailty and showed strong negative correlation with grip strength. Since low grip strength is a component of the Fried physical frailty phenotype, AGT, KG, and AT levels may serve as potential biomarkers for monitoring frailty onset and progression. Future longitudinal studies based on serum samples will be essential for identifying frailty biomarkers, therapeutic targets, and developing interventions.

4 Frailty Metabolomic Biomarkers

As the final downstream products of gene expression, metabolites are considered the most effective functional and signaling molecules reflecting cellular metabolic activity and biological phenotypes, increasingly linking to functional omics. Frailty is frequently accompanied by metabolic disturbances in energy, muscle, inflammation, and hormones, particularly involving nutritional deficiencies, energy imbalance, and lifestyle-related pathway dysregulation. Research on metabolism-related biomarkers may thus provide novel insights for frailty interventions.

4.1 Glucose Metabolism Disorder

Glucose is the most important energy substrate for the organism, and its metabolic disruption can cause energy supply imbalance and reduced insulin sensitivity, closely associated with frailty. Westbrook et al. found elevated levels of glycolysis, tricarboxylic acid (TCA) cycle, and TCA cycle-derived neurotransmitters (glutamate and GABA) in frail older adults. This may occur because TCA cycle metabolites can be transported from mitochondria to cytoplasm and plasma via dicarboxylate transporters and other mechanisms, thereby affecting overall health status.

4.2 Lipid Metabolism Dysregulation

Lipid metabolism influences frailty development by regulating skeletal muscle mass and function. With the rise of metabolomics, untargeted serum metabolomics has been increasingly applied to investigate lipid metabolic characteristics in frail older adults. A British aging cohort study analyzing untargeted serum metabolites in 1,191 older individuals identified 12 frailty phenotype-associated metabolites, including three tocotrienols and six carnitines. Network enrichment analysis and statistical modeling identified carnitine shuttle and vitamin E metabolism as two major pathways associated with frailty. Subsequently, positive associations between frailty and five metabolites including serum ceramides, cholesterol, and phosphatidylcholine were confirmed, with plasma lysophosphatidylcholine content also used to predict frailty phenotypes such as gait speed decline. Further research suggests that lipid metabolism dysregulation may affect frailty through mitochondrial electron transport chain dysfunction and declines in muscle mass and function. Future studies should continue exploring novel insights regarding abnormal lipid metabolism and frailty development in older adults.

4.3 Amino Acid Metabolism Disorder

Beyond protein synthesis, amino acids serve as precursors for various bioactive molecules and influence muscle atrophy and dysfunction by modulating nutritional status, inflammation, insulin sensitivity, and redox homeostasis. Consequently, amino acid metabolism disorders play an important role in frailty pathogenesis. Calvani et al. found that patients with physical frailty and sarcopenia (PF&S) exhibited higher serum levels of asparagine, aspartate, ethanolamine, glutamate, citrulline, sarcosine, and taurine, along with lower serum α-aminobutyrate and methionine concentrations, indicating links between PF&S and energy metabolism. Other studies propose that elevated circulating amino acids (such as valine, leucine, isoleucine, tryptophan, serotonin, and methionine) serve as biomarkers for muscle mass decline and frailty in older adults. Frail older adults may transition from an anabolic state in middle age to a catabolic state in older age, resulting in elevated serum amino acid levels. Therefore, in-depth serum metabolomics studies investigating amino acid-related metabolic pathways in frail older adults may reveal potential metabolic changes and pathological mechanisms.

4.4.1 Sex Hormones

Key hormones potentially influencing frailty include free testosterone (FT), dehydroepiandrosterone (DHEA), and beta-estradiol (E2). The impact of circulating testosterone levels on frailty differs by sex, with age-related declines occurring to varying degrees in both genders. Hsu et al. demonstrated that age-related FT decline is associated with components of frailty including reduced energy, muscle strength, and physical function. Six-month FT treatment in frail older men can prevent age-related lower limb muscle strength loss and improve body composition, quality of life, and physical function. DHEA, a precursor of androgens and estrogens, regulates bone metabolism, influences physical performance, and improves cognitive function in frail patients. Reduced DHEA levels correlate with increased frailty prevalence, and DHEA supplementation can improve musculoskeletal symptoms and enhance physical function. Carcaillon L et al. found that endogenous E2 levels decrease significantly with age and education but increase with body mass index, CRP, and impaired activities of daily living, suggesting potential as a serological frailty marker.

4.4.2 Other Hormone Metabolism

Serum growth hormone (GH) and insulin-like growth factor 1 (IGF-1) levels gradually decline during frailty progression, primarily through the GHRH/GH/IGF-1 axis. IGF-1, the main effector of GH, serves as an endocrine mediator of growth and development under physiological conditions and plays important roles in immune and inflammatory regulation. Decreased IGF-1 secretion predisposes to neuronal aging and sarcopenia, both core components of frailty.

4.5 Oxidative Stress Level Dysregulation

In older adults, frailty is associated with elevated oxidative stress markers and reduced antioxidant parameters. Oxidative stress may cause musculoskeletal system damage, promoting frailty and slow gait progression. Vitamin E, an antioxidant, shows an inverse relationship with frailty, and its decline may increase reactive oxygen species (ROS)-mediated cellular damage. Kameda et al. identified 15 serum biomarkers in frail individuals, including seven antioxidant-related metabolites (acetylcarnosine, ERG, S-methyl-ERG, trimethylhistidine, OA, 2-ketobutyrate, and urate) and three amino acids with free radical scavenger properties (methionine, proline, and tryptophan). Liu et al. found in a prospective cohort study that serum isoprostanes, osteoprotegerin, and lipoprotein-associated phospholipase A2 (LpPLA2) are biomarkers of increased oxidative stress in community-dwelling frail older adults. Therefore, reducing oxidative stress represents a potential therapeutic target, and future research should investigate whether oxidative stress-reducing interventions can prevent or treat frailty.

Frailty represents age-related physiological homeostatic imbalance that can be reversed through early identification and intervention in clinical practice. However, no specific, stable, and reliable frailty biomarkers have been identified to date. The advent of omics platforms has enabled widespread application of biomarkers in frail populations and advanced research in this field. This review summarizes advances in frailty biomarker research across epigenomics, transcriptomics, proteomics, and metabolomics, contributing to early frailty identification, effective intervention development, and frailty prevention in older adults.

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Conflict of Interest: The authors declare no conflict of interest.

Literature Search Strategy: Chinese databases (Wanfang Data and CNKI) were searched using keywords "衰弱, 衰弱早期, 表观基因组学, 转录组学, 蛋白组学, 代谢组学, 生物标志物" (frailty, pre-frailty, epigenomics, transcriptomics, proteomics, metabolomics, biomarkers). English databases (PubMed and Web of Science) were searched using keywords "frailty, pre-frailty, epigenomics, transcriptomics, proteomics, metabolomics, biomarkers." The search period covered database inception to July 2022. Inclusion criteria: systematic reviews, guidelines, meta-analyses, and original studies related to early-stage multi-omics biomarkers of frailty in older adults. Exclusion criteria: conference abstracts and articles without full-text availability.

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